EFFICACY OF TENOFOVIR DISOPROXIL FUMARATE COMPARED WITH ENTECAVIR TO TREAT CHRONIC HEPATITIS B VIRUS MONOINFECTION PATIENTS

Saira Saleem*, Naila Iqbal, Sundas Shabbir***, Firdous Iqbal****, Lubna Ghazal*****, Fatima Tuz Zahra******

*Tehsil Head Quarter Hospital, Pindigheb, Attock, Pakistan
**Izzat Ali Shah Hospital, Wah Cantt, Rawalpindi, Pakistan
***Quetta Institute of Medical Sciences, Quetta, Pakistan
****Al-Aleem Medical College, Lahore, Pakistan
*****Wah Medical College Wah Cantt, Rawalpindi, Pakistan
*****Armed Forces Institute of Pathology (National University of Medical Sciences), Rawalpindi, Pakistan

ABSTRACT

Objectives: To assess the efficacy among tenofovir disoproxil fumarate (TDF) and entecavir (ETV) in the treatment of chronic hepatitis B monoinfection patients.

Material and Methods: A cross sectional analytical study carried out at District Headquarter Hospital Attock between January 2019 to July 2020. Total 120 chronic HBV patients with quantitative PCR having DNA viral load > 20,000 IU /ml after the treatment failure with any other Nucleos(t)ide Analogues (Lamivudine, Adefovir, Telbivudine) or PEG-IFN (peglyated interferon) were considered. The patients were sorted in two groups, 60 were given TDF (group 1) and 60 were given entecavir (group 2) for a period of 6 months. Follow up carried out after 24 weeks by comparing HBV-DNA levels to compare efficacy between two drugs. Assessment of treatment eligibility for chronic HBV mono-infection is formed by investigating the extent of existing liver disease by ultrasound examination, complete blood count (CBC), liver function tests (LFTs) and Aspartate aminotransferase to platelets ratio index (APRI) score.

Results: Range for age of patients was 15~65 years, divided further into three groups 15~19 years 12(10%), 20~60 years 84(70%) and 61~65 years 24(20%). The gender distribution based on these groups was 84(70%) males and 36(30%) females. After 6 months of treatment with TDF / entecavir drugs, compensated liver with better prognosis was showed by TDF 60(50%) and decompensated liver 19(15.8%), cirrhosis 29(24.2%), and fibrosis 12(10%) by entecavir with significant p value <0.001. Post treatment virological response (HBV-DNA levels) at 24 weeks was markedly higher among group 1 (TDF treatment) rather than group 2 (ETV treatment) i.e. 53(88.3%) and 42(70%) respectively.

Conclusion: Efficacy of TDF is better than ETV for treatment of chronic HBV monoinfection patients.

Key Words: APRI score, Chronic HBV, Entecavir, Tenofovir disoproxil fumarate.

This article can be cited as: Saleem S, Iqbal N, Shabbir S, Iqbal F, Ghazal L, Zahra FT. Efficacy of tenofovir disoproxil fumarate compared with entecavir to treat chronic hepatitis B virus monoinfection patients. Pak J Pathol. 2022; 33(1): 9-13.

DOI: 10.55629/pakjpathol.v33i1.667.

INTRODUCTION

Hepatitis B virus (HBV) represents a prime worldwide risk to human well-being and health. Around 0.4 billion people are suffering from chronic HBV and roughly one million people die every year because of chronic HBV complications, worldwide [1]. The mode of transmission of HBV varies in different geographic areas. Maternal to fetal transmission is predominant in high prevalence areas. While in intermediate prevalence areas, horizontal transmission is more common and unprotected sexual intercourse is substantial means of transmission in low prevalence areas [2].

Correspondence: Dr Naila Iqbal, Consultant Pathologist and Senior Lecturer, Izzat Ali Shah Hospital/ Wah Medical College, Wah Cantt, Rawalpindi, Pakistan.

Email: **dr.naila.ahmad@gmail.com**

Received: ***14 Mar 2021****; Revised:* ***07 Dec 2021****; Accepted:* ***27 Dec 2021***

Array of clinical symptoms of HBV is from asymptomatic carrier to hepatocellular carcinoma (HCC). Disease progression depends upon combined host and viral factors, including the host immune response, alongwith age, sex, viral load, viral genotypes and environmental factors [3].

Chronic HBV disease is characterized by the persistence of HBsAg in the blood for over a half year. There are different stages of liver disease depending upon different guidelines with minor differences i.e. American Association for study of liver diseases (AASLD), European Association for study of Liver (EASL) and Asian Pacific Association for study of Liver (APASL) [4]. Cirrhosis and end-stage liver disease or HCC are most serious and life-threatening complications of chronic HBV infection. The disease prevalence, quantification of disease burden and its prevention and control is required in general population all over the world [5].

The indication for antiviral therapy mainly depends upon severity of liver damage, HBV viral load and ALT levels. Chronic HBV patients with HBeAg-positive or -negative, determined by HBV DNA [2,000 IU/ml], ALT [ULN] and/or at least with early fibrotic/ fibrotic changes, should be considered for treatment. However, regardless of HBV DNA and ALT levels, anti-viral therapy is required for the patients with compensated or decompensated cirrhosis. Patients having HBV DNA [20,000 IU/ml] and ALT [2xULN] must be treated, despite of the degree of fibrosis. Family history of HCC, cirrhosis and extrahepatic manifestations is suggestive of treatment, even if the typical treatment signs are not present. While, HBeAg-positive chronic HBV patients, defined by persistently normal ALT and increased viral load, require treatment assuming that the age is more than 30 years inspite of the severity of liver inflammation and fibrosis [6]. The main target of remedial treatment is to enhance life span and standard of living by suppressing disease progression as well as HCC development.

Presently, seven anti-virals are being administered for chronic HBV treatment. i.e. interferons (standard and pegylated), and nucleos (t)ide analogues (lamivudine, telbivudine, entecavir, adefovir, and tenofovir). These treatments restrain HBV repeatability as well as improve hepatic inflammation, but nevertheless wipe out HBV. IFN therapy is given for short interval of time, whereas nucleos(t)ide analogues are recommended for long times or even lifelong. Long term treatments may lead to adverse drug effects, resistance development to the drug and inflated expenses. Hence, evidence-based guidelines are required to be established for appropriate treatment of chronic HBV [7].

Among all, tenofovir is the most powerful drug with high resistance barrier, significantly reduces viral load and ALT levels, declines HCC incidence among patients without cirrhosis and lessens the mortality rate in patients with acute on chronic liver failure which is a good predictor of survival [8].

Our objective is to analyze the viability of both drugs; TDF and ECV, and their effects on chronic HBV mono-infection patients.

MATERIAL AND METHODS

It was a cross-sectional analytical study, carried at District Head Quarter (DHQ) hospital Attock. Time duration was from January 2019 to July 2020. It was approved by ethical research committee of DHQ hospital, Attock. Chronic HBV patients with quantitative PCR having DNA viral load >20,000IU /ml after the treatment failure with any other Nucleos(t)ide Analogues (Lamivudine, Adefovir, Telbivudine) or PEG-IFN (peglyated interferon) were included. Patients responding to any other Nucleos(t)ide Analogues (Lamivudine, Adefovir, Telbivudine) or PEG-IFN, prior to use of TDF as a monotherapy for minimum 6 months were excluded. The purpose of our study is to compare the effectiveness of TDF and ECV for the medical treatment of patients with chronic HBV mono-infection.

This study comprised of 210 patients with chronic HBV monoinfection. However, 50 patients having viral load <20,000 IU /ml were excluded. Out of remaining 160 chronic HBV patients, 40 patients having no previous failure to any nucleos(t)ide analogues were also excluded. Hence, 120 patients out of total 210 chronic HBV patients fulfilling the inclusion criterion were further investigated in our study.

Total 120 patients, having the previous failure to any other Nucleos(t)ide Analogues (Lamivudine, Adefovir, Telbivudine) or PEG-IFN were categorized in two groups. 60 patients were included in each group. Group 1 was administered TDF as a monotherapy for 6 months, whereas, group 2 was given entecavir therapy for 6 months.

In this study, patients were assessed for treatment eligibility having chronic HBV mono-infection based upon APRI score using national guidelines provided by Hepatitis control program Directorate General Health Services Punjab, recognized by World Health Organization (WHO). Initiation of anti-viral therapy was prioritized among individuals of all ages who had chronic hepatitis B disease and cirrhosis based on APRI score >2. If APRI score was between 0.5~2, then anti-viral therapy was recommended to the patients with persistent abnormal ALT (males > 30 IU/L, females > 20 IU/L) or viral load > 20,000 IU/ml. If APRI score was < 0.5, no treatment was recommended and the patients were only reassured/ reassessed.

Data analysis was carried out in SPSS version 24. For qualitative data, gender and age distribution was established. Also, the frequencies and percentages of staging of liver fibrosis by ultrasound were calculated and comparison was done by applying chi-square test. For APRI scoring two quantitative variables; platelets and liver function tests comparison was performed by independent T-test, applied with significant p value <0.05.

RESULTS

Male patients 84 (70%) were more than female 36(30%), out of total 120 chronic HBV patients. Depending upon age distribution, 12 (10%) were between 15~19 years, 84 (70%) were among 20~60 years and 24 (20%) patients were 61~65 years. Table-I depicts the gender and age distribution of patients.

Two groups were formed with 60 patients each. Group 1 were given TDF before the previous failure of any other Nucleos(t)ide Analogues for 6 months, whereas, Group 2 were given entecavir for 6 months. Chronic HBV mono infection patients having early fibrotic/ fibrotic changes at baseline were broadly classified into compensated or decompensated liver disease after treatment. Decompensated liver disease was further categorized into fibrosis, cirrhosis and decompensated chronic liver disease (DCLD).

From the Table-II, it is pertinent that after 6 months of treatment, better prognosis is showed by TDF 60(50%) resulting in compensated liver disease. While with entecavir 60(50%) developed decompensated liver disease i.e. fibrosis 12(10%), cirrhosis 29(24.2%) and DCLD 19(15.8%).

APRI score is a less invasive way to check liver cirrhosis with high degree of accuracy. APRI score, consisting of two quantitative variables platelets and liver function tests, done with significant p value <0.001 as displayed in Table-III, below.

HBV-DNA suppression is a basic determinant of treatment result, and predicts the response to oral antiviral treatment. AASLD recommends that, 24 weeks is a useful time point for monitoring response to oral antiviral therapy. At 4, 12- and 24-weeks HBV-DNA levels were recorded among both groups as shown in Table-IV. High viral response rates were seen in people treated with TDF (Group 1) and entecavir (Group 2) at 24 weeks. The response rate/ HBV-DNA suppression was predominant in Group 1 as compared to Group 2 i.e. 53(88.3%) and 42(70%) respectively.

Table-I: Gender and age distribution.

Gender	Age Distribution (Yrs)			Total
	15~19	20~60	61~65	
Males (n=84)	1(0.83%)	79(65.83%)	4(3.33%)	84(70%)
Females (n=36)	11(9.17%)	5(4.17%)	20(16.67%)	36(30%)
Total (n=120)	12(10%)	84(70%)	24(20%)	120(100%)

Table-II: Comparison of liver disease by ultrasound.

Drug	Decompensated liver disease			Compensated liver disease	Total	p-value
	Fibrosis	Cirrhosis	DCLD			
Entecavir (n=60)	12 (10%)	29 (24.2%)	19 (15.8%)	0(0%)	60 (50%)	
Tenofovir (n=60)	0 (0%)	0 (0%)	0 (0%)	60 (50%)	60 (50%)	<0.001
Total (n=120)	12 (10%)	29 (24.2%)	19 (15.8%)	60 (50%)	120 (100%)	

Table-III: APRI score consisting of two quantitative variables platelets and liver function test.

Variables	T-test	Diff	Significance	Mean Difference	95%Confidence Interval Lower	95%Confidence Interval Upper
Platelets	43.856	119	.000	145.25	138.69	151.81
Liver function test (AST)	24.424	119	.000	41.47	38.11	44.84

Table-IV: Virological Response at 24 x Weeks (6x Months)

	Entecavir (n=60)	TDF (n=60)
Pre-treatment HBV-DNA level (log_{10} IU/mL)	6.74 ± 1.54	7.23 ± 1.22
Total Virological Response in chronic HBV patients		
Undetectable HBV-DNA (%)	**Entecavir**	**TDF**
4 weeks	0 (0/60)	5% (3/60)
12 weeks	33% (20/60)	43% (26/60)
24 weeks	70% (42/60)	88% (53/60)
Post-treatment HBV-DNA level (log_{10} IU/mL)	4.57 ± 1.13	3.13 ± 1.02
Patients with No Response after 24 x Weeks	30% (18/60)	12% (7/60)

*DNA level is mentioned as mean ± standard deviation

DISCUSSION

The key goal of antiviral medication is to restraint replication of virus. This is achieved when HBeAg positive chronic HBV patients become HBeAg negative and concealment of HBV DNA quantification has occurred. In this research, two equal groups of patients were selected. One group was given entecavir while the other group was given tenofovir

disoproxil fumarate. These two drugs have strong antiviral action and low resistant rates. This study reveals that, group of patients treated with entecavir experienced decompensated liver status, raised LFTs and increase viral load based on PCR. While on the other hand, group of patients treated with tenofovir disoproxil fumarate show better prognosis, experience compensated liver disease, possess huge decrease in viral load and rectification in liver functions. This research study is in concordance with a study carried out in Italy comparing the viability of these two antiviral medications and achieving better results with tenofovir disoproxil fumarate [9].

Out of total 120 patients, we divided them into 2 cohort groups. 60 patients were included in each group. The age distribution was classified as 15~19 years, 20~60 years and 61~65 years. Gender distribution was performed and frequencies recorded as 70% and 30% for males and females, respectively. According to APRI score and comparison of liver disease by ultrasound, two drug groups have very high significant correlation with p value <0.001 Consistent with the studies performed in Taiwan and Germany [10, 11], our study reveals that, TDF is superior to entecavir with respect to anti-viral efficacy observed with serum HBV-DNA loads among chronic HBV mono-infection patients.

Naive patients who begin therapy and start utilizing nucleos(t)ide analogue for example ETV and TDF, these two antiviral drugs establish potent antiviral effect and low level of resistance. Patients, who had prior exposure or develop resistance to other nucleos(t)ide analogues, TDF is the best choice to initiate. The only side effect observed by TDF is renal impairment and osteoporosis [12].

TDF is used in chronic HBV regardless of HBeAg level, prior use of other resistant nucleos(t)ide analogue and presence/ absence of cirrhosis. TDF effectively decreases HBV DNA levels, reduces ALT levels, prevents HBV reactivation or exacerbation and lessens the risk of HCC. TDF is safe drug in pregnancy and lactating mothers as well as in patients with normal renal functions [13]. According to AASLD, viremia is decreased in patients after completing course of 96 weeks with TDF and entecavir, and after 48 weeks of treatment most of the HBeAg positive patients become negative. [14] It is essential to counsel people suffering from chronic HBV to prevent worsening of liver disease and reduce transmission to others. Furthermore, screening of high-risk individuals is mandatory [15, 16].

The main objective of chronic HBV treatment is to decrease HBV DNA levels, sero-conversion, increasing long term viral suppression and avoiding drug resistance. Unfortunately, none of these goals has been achieved with combination therapy, so we focused on monotherapy as compared to combination therapy. In our study, we conclude that chronic HBV mono-infection can be treated by using tenofovir disoproxil fumarate with daily dosage of 300 mg, which is more potent as compared to entecavir given 0.5mg once daily and increased to 1mg in decompensated liver disease.

CONCLUSION

Patients treated with tenofovir disoproxil fumarate show better prognosis, experience improvement in liver function and effective HBV-DNA suppression. Hence, anti-viral efficacy of tenofovir disoproxil fumarate is better than entecavir for treatment of chronic HBV monoinfection patients.

AUTHOR CONTRIBUTION

Saira Saleem: Original concept and study design.
Naila Iqbal: Data analysis, paper write-up and critical revisions.
Sundas Shabbir: Data analysis & results interp-retation.
Firdous Iqbal: Results interpretation and discussion.
Lubna Ghazal: Manuscript review and critical revisions.
Fatima Tuz Zahra: Manuscript review and critical revisions.

REFERENCES

1. Who.int. 2021. Fact sheets. [online] Available at: <https://www.who.int/news-room/fact-sheets>.
2. Kim S, Seo Y, Lee H, Kim M, Lee Y, Lee H *et al*. A multicenter study of entecavir vs. tenofovir on prognosis of treatment-naïve chronic hepatitis B in South Korea. J Hepatol. 2019;71(3):456-64.
3. Biswas A, Panigrahi R, Pal M, Chakraborty S, Bhattacharya P, Chakrabarti S, *et al*. Shift in the hepatitis B virus genotype distribution in the last decade among the HBV carriers from eastern India: Possible effects on the disease status and hbv epidemiology. J Med Virol. 2013;85(8):1340-47.
4. Kwon H, Lok A. Hepatitis B therapy. Nature Reviews Gastroenterol & Hepatol. 2011;8(5):275-84.
5. Wright T. Introduction to chronic hepatitis B infection. Am J Gastroenterol. 2006;101:S1-S6.
6. Shi Y, Shi C. Molecular characteristics and stages of chronic hepatitis B virus infection. World J Gastroenterol. 2009;15(25):3099.
7. Terrault N, Bzowej N, Chang K, Hwang J, Jonas M, Murad M. AASLD guidelines for treatment of chronic hepatitis B. Hepatol. 2015;63(1):261-83.
8. Marcellin P, Wong D, Sievert W, Buggisch P, Petersen J, Flisiak R, *et al*. Ten-year efficacy and safety of

tenofovirdisoproxil fumarate treatment for chronic hepatitis B virus infection. Liver Int. 2019;39(10):1868-75.
9. Lampertico P, Chan H, Janssen H, Strasser S, Schindler R, Berg T. Review article: long-term safety of nucleoside and nucleotide analogues in HBV-monoinfected patients. Aliment Pharmacol Ther. 2016;44(1):16-34.
10. Liaw Y. Reversal of cirrhosis: An achievable goal of hepatitis B antiviral therapy. J Hepatol. 2013;59(4):880-81.
11. van Bömmel F, de Man R, Wedemeyer H, Deterding K, Petersen J, Buggisch P, *et al*. Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/ nucleotide analogues. Hepatol. 2009;51(1):73-80.
12. Buti M, Gane E, Seto W, Chan H, Chuang W, Stepanova T *et al*. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: A randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1(3):196-206.
13. Köklü S, Tuna Y, Gülşen M, Demir M, Köksal A, Koçkar M, *et al*. Long-term efficacy and safety of lamivudine, entecavir, and tenofovir for treatment of hepatitis B virus–related cirrhosis. Clin Gastroenterol and Hepatol. 2013;11(1):88-94.
14. Lim Y, Yoo B, Byun K, Kwon S, Kim Y, An J *et al*. Tenofovir monotherapy versus tenofovir and entecavir combination therapy in adefovir-resistant chronic hepatitis B patients with multiple drug failure: Results of a randomised trial. Gut. 2015;65(6):1042-51.
15. Marrero J, Kulik L, Sirlin C, Zhu A, Finn R, Abecassis M, *et al*. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 Practice Guidance by the American Association for the study of liver diseases. Hepatol. 2018;68(2):723-50.
16. Galle P, Forner A, Llovet J, Mazzaferro V, Piscaglia F, Raoul J, *et al*. EASL clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182-36.