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"COMPARATIVE EFFICACY OF ENTECAVIR AND TENOFOVIR ALAFENAMIDE IN TREATMENT OF CHRONIC HEPATITIS-B "

Medicine

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ABSTRACT

Aims: The Aim of study is to compare the efficacy of entecavir with tenofovir alafenamide in treatment of Chronic Hepatitis B patients.
Materials and methods: It is a prospective cohort study to compare efficacy of ENTECAVIR and TAF in treatment of Chronic Hepatitis B. Study location was Out Patient Department(OPD), In Patient Department(IPD) and Medical Intensive care unit (MICU) of Dept. of Medicine of DMCH, Laheriasarai. Study duration was 12 months and total 50 individual was in this study.
Result: 12% patients of Entecavir and 16% patients of TAF group were presented with HTN; while DM was observed in 4% patients of Entecavir and 8% patients of TAF group. Regarding co-morbidities we found no significant difference between two groups (p value = >0.05). Hepatitis B virus DNA in the HBeAg positive group was approximately 2 log10 IU/mL higher than in the HBeAg-negative group.
Conclusion: Treatment with antiviral therapy, ETV or TAF, showed potent antiviral activity against HBV and the efficacy of both drugs was comparable.TAF and ETV showed comparable efficacy and safety in treatment-naïve CHB patients.

KEYWORDS

Chronic hepatitis-B, HBV and HBeAg.

INTRODUCTION

Hepatitis B virus (HBV) infection continues to remain a significant global health problem. Estimates of the World Health Organization (WHO) suggest that more than 2 billions people worldwide have been infected with HBV. Of these, approximately 240 million individuals have chronic (long-term) liver infections and at risk of serious illness and death, mainly from liver cirrhosis and hepatocellular carcinoma (HCC). More than 780 000 people die every year due to the acute or chronic consequences of hepatitis B.[1]

Since India has one-fifth of the world's population, it accounts for a large proportion of the worldwide HBV burden. India harbors 10–15% of the entire pool of HBV carriers of the world.[2] It has been estimated that India has around 40 million HBV carriers. About 15–25% of HBsAg carriers is likely to suffer from cirrhosis and liver cancer and may die prematurely. Infections occurring during infancy and childhood have the greatest risk of becoming chronic. Of the 2.6 Crore (26 million) infants born every year in India, approximately 10 Lakhs (1 million) run the life-time risk of developing chronic HBV infection.

HBV infection is determined by the interplay between virus replication and host immune response. Acute liver damage is caused mainly by the protective immune response, which destroys virus-infected liver cells. In the absence of an immune response sufficient to clear the virus, the infection becomes chronic. This is the case with perinatally acquired HBV infection, which tends to be clinically silent and evolves to chronicity in 95%.[3] Perinatal infection begins with an immunotolerant phase in which virus replication is high with little hepatic damage.[4] In the laboratory this phase is identifiable by the serum virus markers HBsAg and HBeAg and HBV DNA; serum aminotransferases may be normal or slightly raised. It is succeeded, a variable time after infection, by a phase in which an immune response to the virus develops, with resultant liver damage that may progress to cirrhosis. This immunoactive phase is characterized by serum aminotransferase flares and suppression of viral replication (decline in serum HBV DNA). These flares may be associated with development of an antibody to HBeAg, resulting in a low or non-replicative phase in which the virus is suppressed by the host immune system. In some patients an immunoescape phase arises when the virus mutates to variants that do not express HBeAg (HbeAg negative chronic hepatitis). A proportion of these HBeAg-negative patients then show high HBV replication with progression of their liver disease. Some patients ultimately lose HBsAg and this final phase is referred to as resolution of infection.

Adults who are infected with HBV usually develop an acute hepatitis that resolves spontaneously. However, 3-5% go on to develop chronic hepatitis B which then follows a similar pattern to perinatally acquired chronic HBV infection.[4]

Currently there are 2 options for treating Chronic Hepatitis B-Interferon and oral antiviral agent (nucleotide analogues). Treatment with oral anti viral agents is the preferred option because of more successfully maintained viral suppression, fewer long term complications and a more convenient regimen. In particular, second generation nucleotide analogues such as entecavir (ETV), tenofovir disoproxil fumerate (TDF) and tenofavir alafenamide (TAF)are recommended as 1st line therapy for CHB because of their high genetic barrier to resistance and effective viral suppression.

The Aim of study is to compare the efficacy of entecavir with tenofovir alafenamide in treatment of Chronic Hepatitis B patients.

MATERIALS & METHODS

Type of Study: It is a prospective cohort study to compare efficacy of entecavir and TAF in treatment of Chronic Hepatitis B.

Place of Study: Out Patient Department (OPD), In Patient Department (IPD) and Medical Intensive care unit (MICU) of Dept. of Medicine of DMCH, Laheriasarai.

Sample Size: A total of 50 patients of chronic Hepatitis B

All the patients were divided into 2 groups of both sexes. One group was treated with Entecavir and the other was treated with TAF.

Duration of Study: 12 months

Inclusion Criteria:
- Patients aged >14 years.
- Both sexes
- Patients with chronic Hepatitis B.

Exclusion Criteria:
- Patients aged <14 years.
- Patients with pregnancy
- Patients of chronic Hepatitis B with HIV
- Patients of acute Hepatitis B
- Active alcoholics

RESULT AND DISCUSSION

Hepatitis B virus (HBV) infection is a severe health problem, which affected more than 400 million people worldwide. After its chronic

infection, about 25% people may develop end-stage liver disease (ESLD), cirrhosis, liver failure, or hepatocellular carcinoma (HCC).[5] At least 391 million people, or 5% of the world's population, had chronic HBV infection as of 2017, and more than 1 million patients were first discovered. Over 750,000 people die of CHB each year. About 300,000 of these are due to liver cancer. So CHB is a thorny problem, especially in less developed countries.[6]

The goals of anti-HBV treatment are to improve quality of life and survival of the infected person by maximally suppressing HBV replication, reducing hepatic necroinflammation and hepatic fibrosis, and delaying and decreasing hepatic failure, progression of hepatic decompensation, HCC, and other complications. Thus, the sustained suppression of HBV replication should be considered the most important therapeutic goal for CHB patients in clinical settings.

Patients with CHB need long-term antiviral treatment. Currently, there is no clear drug withdrawal guideline for antiviral treatment.[7] It is generally believed that antiviral drugs require long-term or even lifelong oral administration to achieve the goal of controlling CHB.[7]

Currently, front-line drugs for CHB include entecavir (ETV) and tenofovir mainly, tenofovir is further divided into tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF).[8] Suppressing hepatitis B virus is nearly a lifelong undertaking. For the patients without treated (nucleos(t)ide analogue-naive), it is important to choose their first drug that is right for them. Soin the choice of drugs, we pay more attention to the efficacy and safety of these drugs.[9]

At present, there is still a lack of relevant systematic research on the efficacy and safety of these drugs for the patients in the treatment of CHB. It is difficult for patients to choose which drug to take, the newer, the better; or the more expensive, the better? In this study, the efficacy and safety of ETV and TAF in CHB patients was compared to provide a basis for patients to choose the more appropriate anti-viral drug.

The present study was conducted in the Department of Medicine A total of 50 patients with chronic Hepatitis B were enrolled in the study and divided randomly into two groups consisting 25 patients in each. One group was treated with entecavir and the other was treated with TAF.

In this study, we carried out a randomized controlled trial to compare treatment efficacy and safety of ETV and TAF in nucleoside-naïve CHB patients at 12 months of treatment. Standard CHB efficacy assessments included HBV DNA suppression, ALT normalization, and HBeAg loss or seroconversion in HBeAg-positive patients; HBsAg loss or seroconversion was the ultimate goal. No statistically significant differences were revealed between the two study drugs for all efficacy end-points. The results of our analysis suggested that, in treatment-naïve CHB individuals, ETV and TAF are very effective to suppress HBV DNA throughout 12 months of study.

Of note, in this study, the majority of patients had a VR over 12 months of therapy. Among HBeAg-positive patients, the cumulative VR rates at month 12 in our study are comparable with previous global multicenter trials of 67% and 76%, respectively.

These results were also comparable in HBeAg-negative patients.[10] In this study, ETV and TAF showed similar overall antiviral efficacy both for one year.

However, our subgroup analysis indicated that TAF was significantly better than ETV for suppressing HBV DNA in HBeAg-positive patients, especially with higher HBV DNA levels. There were a few studies which TDF showed more potent antiviral efficacy than ETV in HBeAg positive patients.[11] When comparing our study with these previous studies, the present study included only treatment-naïve patients and who had been adherent to medication therapy for at least one year. Patient adherence may contribute to achieve comparable overall VR at month 12 and during long-term period in both groups.

TAF has the same mechanism of action as TDF and is a nucleotide reverse transcriptase inhibitor. Tenofovir bisphosphonates, the active component of tenofovir, inhibit the viral polymerase by directly competing with the natural deoxyribose substrates and terminating DNA strands by inserting DNA.[12] Hence we consider the previous studies which have compared the efficacy of ETV and TDF.

Several studies have compared the efficacy of TDF and ETV directly. In a follow-up study of 94 patients, Dogan ÜB et al found that the virologic response and tolerability did not significantly differ between these 2 kinds of drugs in the first year of treatment[13] Similar results were confirmed in other studies with a larger population (n=345), or a longer follow-up time (72 weeks). However, in general, studies which directly compared the efficacy of TDF and ETV are lack, and the followup time is not long enough.

We found that after receiving the antiviral treatment of TAF or ETV, the incidence of liver biochemical response, viral response, and HBeAg loss/seroconversion were all not significantly different (all p value >0.05). Compared to interferon that enhances the host immune system to mount defense against HBV, oral NA therapy (including TAF and ETV) confers low HBeAg seroconversion rates.

Ke et al [14] pointed out that pooled HBeAg seroconversion for TDF was similar to the ETV group (24 weeks: 28% vs 29%, RR= 0.86, 95% CI=0.45–1.66; 48 weeks: 16% vs 10%, RR=1.09, 95%CI=0.57–2.11) in a meta-analysis. Generally speaking, TDF and ETV do not greatly influence HBeAg seroconversion for HBV patients. Therefore, it is plausible that TDF and ETV may have yielded lower rates of seroconversion with a marginal host immune system impact for different clinical trial population. As a clinical trial with a longer observation time of 144 weeks, regression of fibrosis has been observed with FIB-4 and APRI, which was coincident with previous results.

In the present study, there were no statistically significant differences between tenofovir and ETV in HBV DNA suppression to undetectable levels till 12 months. When comparing the response rates overall in the patients, our results can be interpreted as ETV and tenofovir treatment being equally effective in CHB patients.

Multi-center, long-term studies using ETV and/or TAF have shown excellent safety and tolerance with little antiviral resistance. In our study, there was no serious clinical adverse reaction in those 2 treatment groups.

In prior studies that evaluated the long-term efficacy of TAF in 131 patients, virological breakthrough was not observed. Resistance to TDF has not been observed through 6 years of continuous use inCHB patients. In another study by Chang et al., ETV resistance emerged in only one patient during 5 years of followup, therefore they suggested extended long-term therapy with ETV through to 5 years in HBeAg-positive CHB.[15]

To date, randomized controlled or well matched comparative studies regarding the efficacy of TAF or ETV in treatment-naïve CHB patients were very rare. Therefore, it is necessary to conduct direct comparisons of a prospective nature with larger numbers of patients and longer period of treatment.

CONCLUSION

At the end of the study we come to the conclusion that:

- Treatment with antiviral therapy, ETV or TAF, showed potent antiviral activity against HBV and the efficacy of both drugs was comparable.TAF and ETV showed comparable efficacy and safety in treatment-naïve CHB patients.
- Both drugs were safe without significant AEs. We did not find any significant renal toxicity in CHB patients who received TAF or ETV.
- The result of the present study suggested that TAF might be the more potent option in a subgroup of HBeAg-positive CHB, especially with higher HBV DNA levels. We also found TAF is more cost effective than ETV.
- However, a longer period of follow-up is needed to assess the resistance rate and safety profiles of each drug during long-term use.

Table: Distribution of mean Serum HBV DNA level at Baseline and Serum qHBsAg level at Baseline

		Entecavir		Tenofovir Alafenamide		p Value
		Mean	±SD	Mean	±SD	
Serum HBV DNA (log_{10} IU/mL)	$HbeAg^+$	7.79	±0.34	8.07	±0.29	0.002
	$HbeAg^-$	4.92	±0.20	5.16	±0.48	0.025
Serum qHBsAg(log_{10} IU/mL)	$HbeAg^+$	3.66	±0.59	4.54	±0.35	<0.001
	$HbeAg^-$	3.63	±0.66	3.34	±0.44	0.07

Table: Distribution of Co-morbidities, HbeAg, HBV DNA Negativity by PCR at 12 months and ALT normalization at 12 months

		Entecavir		Tenofovir Alafenamide		p value
		Frequency	Percentage	Frequency	Percentage	
Co-morbidities	HTN	3	12.0	4	16.0	0.50
	DM	1	4.0	2	8.0	0.50
HbeAg	$HbeAg^+$	13	52.0	11	44.0	0.78
	$HbeAg^-$	12	48.0	14	56.0	
HBV DNA Negativity	$HbeAg^+$	9	69.2	9	72.7	0.396
	$HbeAg^-$	11	91.7	13	92.9	0.265
ALT normalization	$HbeAg^+$	8	61.5	7	63.6	0.375
	$HbeAg^-$	10	83.3	11	78.6	0.422
Histological Response	$HBeAg^+$	9	69.2	8	72.7	0.396
	$HBeAg^-$	8	66.7	10	71.4	0.433

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