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Outcome of Hepatitis B treatment with oral drugs (Tenofovir and Entecavir) in a tertiary care center in eastern India

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Abstract

Background and Aim. *Hepatitis B virus (HBV) infection remains a major public health threat in India, despite the availability of effective vaccination against the virus, and is one of the most significant chronic viral infections affecting the Indian population. There are very few reports on the outcome of hepatitis B treatment with oral drugs which this study has stressed on.* ***Patients and Methods.*** *This prospective study included 134 patients with chronic HBV patients on oral antiviral therapy (Tenofovir or Entecavir) for at least 1 year. Viral loads were assessed by HBV-DNA Quantitative assay. Clinical history included mode of transmission, physical examination, laboratory investigations included liver function test, complete CBC, and serum creatinine were done. Non-invasive markers of liver fibrosis included APRI, FIB-4, and fibroscan were assessed at baseline and 24th month.* ***Results.*** *Vertical transmission was the most common mode of transmission noted in 26.11%, followed by blood transfusion in 5.97% of cases. The mode of transmission was unknown in 60.44% of cases. Tenofovir and Entecavir lead to effective viral suppression, with 65.7% of cases (88 out of 134) achieving a viral load below detectable limit (BDL) at the end of 6 months. By the end of the 12th and 18th months, 77.6% (104 cases) and 85.1% (114 cases) respectively achieved viral load BDL. At the end of 2 years, 89.6% (120 cases) achieved viral load below detectable limit. Significant improvements in serum transaminases and liver fibrosis were observed at 24 months post-initiation of therapy.* ***Conclusion.*** *Treatment with Tenofovir or Entecavir in Indian patients with chronic HBV infection is effective in improving hepatic transaminases and fibrosis. Good compliance with these medications, along with regular follow-up, can help prevent the progression of the disease to end-stage liver disease.*

Introduction

Hepatitis B virus (HBV) infection is a major global health issue, with a high prevalence in India. Chronic hepatitis B virus (CHB) infection is a condition characterized by ongoing HBV replication, leading to the progression of liver disease. This can result in serious complications such as hepatic decompensation, cirrhosis, and hepatocellular carcinoma (HCC). The main objective of treatment is to control HBV replication to reduce liver inflammation and prevent the advancement of liver disease[1].The epidemiology of HBV in India has become significant not only on a national level but also globally, with the potential for India to soon have the largest population of HBV-infected individuals in the world. Despite the availability of effective vaccination against the virus, HBV continues to pose a major public health threat in India and remains one of the most significant chronic viral infections affecting the population. In India, HBV is a leading cause of hepatocellular carcinoma[2]. Chronic HBV infection progresses through various phases, each of which maintains a dynamic equilibrium with the others. This balance is determined by the closely integrated interaction between the virus and the host's immune response[3]. Nucleos(t)ide analogues (Nuc) can quickly suppress HBV replication, normalize serum transaminases, restore liver function, and improve survival rates for patients with hepatic decompensation. Long-term Nuc therapy can also significantly improve liver health, reverse advanced fibrosis, and slow disease progression, including the development of HCC[4]. There are very few reports on the outcome of hepatitis B treatment with oral drugs from eastern India. In this study, we tried to elaborate on the treatment outcome of hepatitis B with oral drugs.

Materials and Methods

This prospective observational study was conducted in a tertiary care setup in eastern India for one year. The study included patients who attended the Tropical Medicine outpatient department or were admitted to the inpatient department with chronic hepatitis B (defined by persistence of HBsAg for more than 6 months) and were on oral antiviral therapy (Tenofovir or Entecavir) for at least 1 year by the end of the study. Patients having other chronic liver diseases were excluded such as chronic HCV infection, combined HBV and HCV infection, HIV infection and patients with Metabolic Dysfunction-Associated Steatotic Liver Disease. Included patients were interviewed for basic demographics and medical history. Clinical examinations were conducted for jaundice, hepatomegaly, other organomegaly, stigmata of chronic liver disease (CLD), and other system examinations.

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Laboratory investigation

Included liver function test (LFT), complete CBC, serum urea, and creatinine. Viral serology included HBsAg, HBeAg, anti HCV and anti-HIV. Prothrombin time was assessed where needed. Ultrasonography of the upper abdomen, HBV-DNA Quantitative assay, and Fibroscan were done. The initial diagnosis of the cases was by HBsAg test by ELISA method. Those who tested positive were evaluated further by HBV DNA PCR. The lower limit of detection was 12 IU/ml. Chronic hepatitis C was excluded by anti-HCV serological test. Serum iron profile, serum ceruloplasmin, urinary copper, and other tests were done to rule out Wilson's disease/ hemochromatosis/hemosiderosis as needed. None of the patients had uncontrolled diabetes, so metabolic dysfunction associated fatty liver disease could be possibly excluded. APRI (AST to Platelet Ratio Index) and FIB-4 scores were used as non-invasive tools for assessment of liver fibrosis. APRI and FIB-4 were calculated by the following formulae[5]. APRI= (AST/ULN)×100)/platelet count (10^9/L); ULN= Upper limit of normal. FIB-4= (age (yr)×AST (IU/L))/(platelet count (10^9/L x [ALT (IU/L)1/2]). Transient elastography (Fibro-Scan) are performed to rule out advanced fibrosis using Fibro-Scan (FibroScan Expert 630 Machine; Echosens, Paris, France). For classification the following cut-off values were used: F0/F1/F2 ≤ 10.2 kPa; F3> 10.2 kPa; and F4> 16.3 kPa[6].

Statistical analysis

Descriptive data was represented as mean, standard deviation, range, frequency, or percentages, as applicable. Continuous variables were compared using the student t-test. A p-value of less than 0.05 was considered significant. Categorical variables were analyzed using the Chi-square test (χ^2). Analysis for various measures was performed using various standard statistical software packages like Microsoft Excel and Graph-Pad Prism.

Results

The study included a total of 134 cases. The mean age of the study population was observed as 39.66±12.65 years; with 28.66% cases belonging to the age group of 31-40 years, followed by 23.13% cases belonging to the age segment of 41-50 years and 21.64% belonging to 21-30 years. 61.94% (n=83) were male patients. 8.96% of patients were alcohol users and 6.72% of patients were smokers. Among comorbidities, 25 cases had hypertension and 12 had diabetes mellitus. While the mode of transmission was unknown in 60.44% of cases, vertical transmission was the most common mode of transmission noted in 26.11% followed by blood transfusion in 5.97% of cases. The mode of diagnosis was incidental in 21.64% of cases, followed by 19.4% vide family screening and 18.65% through pregnancy screening, **table 1**. Mean viral loads were noted at prospective time points, **table 2**. Mean SGOT and SGPT levels significantly decreased over time frame. While the baseline SGOT was recorded as 53.65, SGOT significantly decreased to 29.91 after 24 months at p<0.001. SGPT decreased from 60.11 at baseline to 32.26 after 24 months at p<0.001, **table 3 and table 4** illustrate a gradual decrease in viral load distribution over time. At the end of 6 months, 65.7% of cases (88 out of 134) achieved a viral load below the detectable limit (BDL). This percentage increased to 77.6% (104 cases) at the end of 12 months and further to 85.1% (114 cases) at the end of 18 months. By the end of 2 years, 89.6% (120 cases) achieved viral suppression with a viral load below the detectable limit. At baseline, 25 cases had HBeAg Reactive, which was reduced to 6 at the end of 24 months. Alpha-fetoprotein levels were found to be high (>40ng/ml) in 2 cases. In one case, on evaluation by triphasic CT scan, the patient was diagnosed with hepaticellular carcinoma. Noninvasive markers of liver fibrosis like APRI, FIB-4, and fibroscan were assessed at baseline and 24thmonth, **table 5**.

Table 1: Mode of transmission and diagnosis

Mode of transmission	Number of patients
History of family member-parents being positive (vertical transmission)	35
History of blood transfusion	8
Sexual intercourse	6
History of tattooing	4
Not known	81
Mode of diagnosis	
During jaundice evaluation/symptomatic	24
Pregnancy screening	25
Family screening	26
During blood donation	11
Serology test before surgery	19
Others/ Incidental	29

Table 2: Mean viral load at prospective time points

Baseline	**27144238.31**
6th Month	542578.803
12th Month	165316.8317
18th Month	9337.95122
24th Month	1159.85618

Table 3: Mean biochemical parameters

	Baseline	12th Month	24th Month	P values
SGOT (Mean)	53.65	54.89	29.91	<0.001
SGPT (Mean)	60.11	59.63	32.26	<0.001

Table 4: Viral load distribution (N)

	Baseline	6th Month	12th Month	18th Month	24th Month
BDL	0	88	104	114	120
12 - 99	28	12	8	9	8
100 - 999	26	10	10	4	3
1000 - 99999	49	16	6	4	2
≥100000	31	8	6	3	1

***BDL**: below detectable level*

Table 5: Non-invasive markers of liver fibrosis

Markers		Baseline	24th month	P value
APRI	>2	30	26	0.33
	1.5-2	50	42	
	<1.5	54	66	
FIB-4	>3.25	28	24	0.27
	1.45-3.25	55	46	
	<1.45	51	64	
Fibroscan	>12.5 kPa	26	24	0.68
	8-12.5	52	47	
	<8	56	63	

Discussion

Hepatitis B virus infection is a significant global public health issue, affecting an estimated 296 million people worldwide with 820,000 deaths in 2019. Current therapies, such as nucleos(t)ide analogs, can prevent the progression to cirrhosis and hepatocellular carcinoma but do not completely eliminate the virus or clear HBsAg. Treatment is recommended for patients with cirrhosis, high HBV DNA levels, and active or advanced liver disease[7]. HBV is a small DNA virus from the Hepadnaviridae family, sharing characteristics with retroviruses such as replication through an RNA intermediate and integration into the host genome. These unique traits enable HBV to persist in infected cells[8]. The main goal of treating chronic hepatitis B (CHB) is to prevent liver damage and cancer by stopping the replication of the hepatitis B virus. Entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) are the preferred first-line medications for this purpose. Peg-IFN therapy is less common due to its significant side effects and the requirement for subcutaneous injections. However, ETV, TDF, and TAF do not directly target the cccDNA of HBV-infected hepatocytes, which means that long-term or lifelong treatment is necessary to maintain HBV suppression[9]. Knowledge of treatment outcomes and adverse effects of antiviral therapy is essential for a comprehensive understanding of the disease. This study aimed to evaluate the effectiveness of Tenofovir and Entecavir therapy in patients with chronic HBV infection at a tertiary care center in eastern India. Our study showed that vertical transmission was the most common mode of transmission, observed in 26.11% of cases, followed by blood transfusion in 5.97% of cases. A previous study highlighted the challenges associated with HBV infection during pregnancy, such as the impact of HBV infection on pregnancy, the effect of pregnancy on HBV infection, mother-to-child transmission of HBV, and the management of medications[10]. Vertical transmission of HBV is highly efficient, with rates ranging from 70% to 90% for hepatitis e antigen (HBeAg) positive mothers and from 10% to 40% for HBeAg-negative mothers in the absence of preventive interventions[11]. Addationaly, studies have reported rates of vertical transmission ranging between 1% and 28%[12,13]. Consistent with other studies we found that blood transfusion, history of tattooing and sexual relation are reasonable risk factors for HBV transmission[14,15]. Our study found that both tenofovir and entecavir (ETV) are effective in suppressing the virus, with 65.7% of cases achieving a viral load below the detectable limit (BDL) after 6 months. This percentage increased to 77.6% at 12 months, 85.1% at 18 months, and 89.6% at 2 years. Among the available nucleos(t)ide analogs (NAs), entecavir and tenofovir are recommended as first-line treatments for HBV-related cirrhosis due to their high antiviral efficacy and low rates of resistance[16]. Several observational studies have compared the antiviral responses of tenofovir and entecavir in treating CHB. These studies found no significant differences in the reduction of serum HBV DNA levels and HBV DNA negativity rates between TDF and ETV treatments. A recent meta-analysis also confirmed that there were no significant variations in ALT normalization rates and HBeAg seroconversion rates after 24 weeks and 48 weeks of TDF or ETV therapy[17,18]. Significant improvements in serum transaminases and liver fibrosis were observed at 24 months post-initiation of HBV therapy. ALT is the most direct, sensitive, and economical indicator of liver inflammation, and its elevated level usually

indicates the occurrence of liver inflammatorion[19]. Therefore, in addition to a positive HBV DNA level, abnormal ALT is also required if antiviral therapy is considered[20]. In accordance with our study, in patients with CHB treated with antivirals, virologic responses in which HBV DNA was not detected by PCR or biochemical responses showing ALT normalization were observed[21]. Furthermore, ALT normalization at 12 months was significantly associated with fewer hepatic events although the number of hepatic events excluding HCC was small[22]. Accurate diagnosis of liver fibrosis is essential for evaluating the impact of treatment on disease progression. In our study, we examined the liver stiffness measured by noninvasive biomarkers FIB-4, APRI, and transient elastography. Although there was an improvement in liver stiffness dynamics at 2 years compared to baseline, this improvement was not statistically significant. Previous research has demonstrated that FibroScan, APRI, and FIB-4 values decreased significantly after 3 years of ETV treatment in patients with chronic hepatitis B[23]. This suggests that these noninvasive fibrosis tests could be valuable for monitoring the regression of liver fibrosis and assessing treatment effectiveness during long-term ETV therapy. These findings align with other studies, such as the research conducted by Li et al., which showed a notable decrease in APRI and FIB-4 values after 3 years of ETV therapy in patients with F2-F4 and F4 METAVIR fibrosis stages[24].

Conclusion

Treatment of viral hepatitis B with oral drugs- Tenofovir and Entecavir leads to effective viral suppression with reversal of liver fibrosis to some extent. Compliance to therapy along with regular follow-up can help prevent the progression of the disease to end-stage liver disease.

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