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# An Open Label Prospective Study to Evaluate the Efficacy of Entecavir in HBeAg Positive Treatment Naive Chronic Hepatitis –B Patients in A Tertiary Care Centre in Eastern India

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**ABSTRACT**
**Background:** *Entecavir is a nucleoside analogue drug that has selective anti-hepatitis B virus (HBV) activity. It is indicated for the treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication, persistent elevations in serum aminotransferase and histologically active disease. We conducted a study to evaluate the efficacy of entecavir (ETV) in hepatitis Beantigen (HBeAg) positive- chronic hepatitis B (CHB) treatment naive Indian patients in real life scenario.*
**Method:** *This is a single center open label prospective observational study to evaluate the efficacy of Entecavir in chronic hepatitis B patients. A total of 140 patients were enrolled in the study from January 2015 to December 2016. Parameters were evaluated at baseline and at 12, 24 and 40 weeks of the treatment, Efficacy of entecavir was assessed by evaluating hepatitis B virus DNA (HBV DNA), serum alanine aminotransferase (ALT) and sero-conversion.*
**Result:** *The mean HBV DNA at baseline was 5.99 log [on a base-10 scale] IU/mL which decreased to 2.12 log IU/mL at the end of 40 weeks. Thus there was a mean change of 3.87 log IU/ml which was statistically significant (P<0.0001). Out of 140 HBeAg positive subjects, 50 (35.71 %) had become negative at the end of 40 weeks. Only 10.71% of the patients had normal ALT (<40IU/l) values in the beginning which increased to 100% at the end of 40 weeks.*
**Conclusion:** *Entecavir significantly improves virological, biochemical and serological markers in HBeAg positive treatment naïve chronic hepatitis B patients.*
**Keywords:** *Chronic hepatitis B, Entecavir, (ETV) HBV DNA.*

## INTRODUCTION

Chronic hepatitis B affects an estimated 400 million people worldwide and causes more than 5 million deaths due to complications of chronic infection[1], Nearly 40 million people out of the global HBV infection pool are from India and every year over 100,000 Indians die due to complications associated with chronic infection[2].

Chronically infected patients with prolonged elevated HBV DNA level, elevated ALT level, and presence of HBeAg are at increased risk of developing progressive liver disease, cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC) and death[1].HBV DNA level of more than 2000 IU/ml ($10^4$ copies/ml) is a strong precursor for development of complications like cirrhosis and HCC[3].Patients with chronic HBV infection who have ALT levels that are near the upper limit of the normal range are at a significantly higher risk for complications of cirrhosis and HCC than patients with ALT levels that are less than half the upper limit of the normal range. The highest risk of complication of cirrhosis and HCC occurs in patients with ALT levels that are one to two times the upper limit of the normal range[4].

Seropositivity for HBeAg and/or HBV-DNA>2,000 IU/ml are significant risk factors for cirrhosis and HCC development, even in asymptomatic subjects with chronic HBV infection[5].The goal of treatment is to suppress HBV replication and ensure the loss of HBeAg with ALT normalization at the end of the treatment, thus decreasing progression of the liver disease to cirrhosis and HCC. Drugs approved for HBV treatment include interferon, nucleoside or nucleotide analogs (lamivudine, adefovir, entecavir, tenofovir, and telbivudine) [6].Interferon requires parental administration, and causes many side effects especially in cases of cirrhosis[7].A substantial percentage of patient particularly those with high levels of viral replication did not respond to treatment with interferon alfa alone or after a short course of corticosteroids[8]. Nucleoside and nucleotide analogs are administered orally, they cause more profound HBV DNA suppression. However these drugs are associated with rebound increase of HBV DNA levels or reactivation of hepatitis if discontinued prematurely. In addition, long-term use of these drugs is compromised by the development of resistance[6]. ETV is a potent and selective inhibitor of HBV DNA polymerase[9]. In preclinical studies performed in chronic woodchuck hepatitis virus infections, ETV showed potent and sustained suppression of viral DNA and an absence of both viral rebounds and emerging ETV resistance (ETVr) [10]. ETV reduced the covalently closed circular DNA viral reservoir to undetectable levels and extended the lives of treated woodchucks by preventing HCC[10]. Therapy with ETV in HBeAg-positive CHB patients demonstrated superior histologic, virologic, and biochemical responses compared with lamivudine at 48 weeks[1]. In a study by Leung et al, comprehensive monitoring of genotypic and phenotypic antiviral resistance was performed on 673 ETV treated nucleoside naive HBV patients; only 3% of ETV treated patients exhibited virologic rebound by the end of 96$^{th}$ week[11].

Therefore, we conducted a prospective observational study to evaluate the efficacy of entecavir in seropositive chronic hepatitis B treatment naive Indian population in real life scenario.

## METHODS

### Study design

This is an open label prospective observational study to evaluate the antiviral efficacy of ETV in treatment naive chronic hepatitis B patient conducted in the department of Hepatology at SCB Medical College &Hospital, Cuttack, Odisha. Data were collected on patients with HBeAg positive chronic hepatitis B, enrolled between January 2015 to December 2016. They received 0.5 mg ETV once daily for a period of 40 weeks. The data for 140 patients were analyzed to evaluate the efficacy of ETV. The study comprised of 4 visits, viz. baseline visit and visits after 12, 24, and 40 weeks of treatment. Of the 140 patients enrolled in the study all completed the study and were considered for evaluating efficacy data.

### Patient selection

Patients meeting the following criteria were enrolled in this study: (1) men and women older than 16 years of age (2)patients with compensated liver disease document by elevated serum ALT

levels (3) patients having HBV DNA levels greater than 2000 IU/ml; (4) hepatitis Beantigen (HBeAg) seropositivity (5) nucleoside naive patients; (6) compliant patients, and (7) women of childbearing potential willing to use an acceptable method of contraception to avoid pregnancy during treatment and for 8 weeks after completion of the study.

Patients with the following criteria were excluded: (i) if diagnosed or suspected as hepatocellular carcinoma (HCC), (ii) suffering with any serious disease besides CHB, including heart disease, immunologic disease, malignant tumor, etc, (iii) hypersensitive to nucleoside or nucleoside (acid) analogues or with a history of nucleoside antiviral drug treatment; (iv) evidence of decompensated liver disease; (v)history of drug abuse or alcohol abuse; (vi) pregnant or lactating women and patients not using adequate contraceptive measures.

**Intervention**

Patients received medication as a part of their usual treatment. They were not exposed to any experimental investigations. After enrollment in the study, all patients received 0.5mg of ETV orally on empty stomach once daily for a period of 40 weeks.

**Data Collection**

Data collection was done at baseline (visit 1) and at visits 2, 3 and 4 at initiation i.e. at 12, 24, 40 weeks of treatment The data collected at baseline were demographics, laboratory investigation, co-morbid conditions, concomitant medications and drug allergies. At subsequent visits data useful to evaluate the efficacy of ETV i.e. HBV DNA load, serum ALT and HBeAg were collected.

**Assay Methodology**

Serum HBV DNA was quantified using the taq Man Real-Time polymerase chain reaction. The lower limit of detection was (<20 IU/ml) Serum ALT level was quantified by local laboratory, normal value range 0-40IU/l.)

**Efficacy Analysis**

The efficacy of antiviral therapy of chronic hepatitis B is measured using surrogate markers. These include undetectable levels of HBV DNA, normalization of ALT, and HBeAg serocon-version at the end of 40 weeks.

**Statistical methods & analysis**

The software package used for statistical analysis was SAS software package version 9.1.3.Paired t-test was used for finding changes from any two visits when the data followed normality assumption and Wilcoxon signed rank test was used when data did not follow normality assumption. McNemar's test was used for paired categorical data for finding change between visits.

**OBSERVATION**

**Demographic summary**

Demographics for all the subjects are shown in Table 1. The mean age of subjects was 37.6 years, with 22 years as minimum and 65 years as maximum. There were more male subjects (N=100, 71.43%) than female subjects (N=40, 28.57%). The mean (SD) weight was 60.1 kgs, with a minimum of 46 kgs and maximum of 75 kgs. All patents were HBeAg positive.

**Efficacy analysis**

**HBV DNA (Viral Load)**

Fig 1 depicts the transition in HBV DNA Levels in our patients across the study period. There are no cases with undetectable Levels of HBV DNA at visit one which improved to 3.57% in visit 2, 32.14 % in visit 3 and 64.29% in visit 4 .After considering the logarithmic transformation of the viral load, the mean HBV DNA (log) was gradually decreased from visit 1 (5.986 log IU/ml), to visit 4 (2.120 log IU/ml ) and this is statistically significant. $P<0.05$. It is graphically represented inFig 2.

**Serum ALT levels**

The mean of ALT in visit 1 was 69.7 IU/L ± 25.88 IU/L. It decreased to 41.1 IU/L ± 17.98 IU/L in

visit2, 27.1 IU/L ±5.44 IU/L in visit3 and 24.8 IU/L ± 2.39 IU/L in visit 4.

Thus, there was a mean decrease of 44.90 IU/L ± 25.70 IU/L from the baseline to the end of the treatment at 40 weeks which was statistically significant (P<0.0001).It is observed that the normal ALT level (40 IU/ml) was 10.71% in visit 1, 60.71% in visit 2, 96.43% in visit 3 and 100% in visit 4.

Serocon version of HBeAg - Out of 140 HBeAg positive subjects in visit 1, 50(35.71%) had become negative in visit 4.Table 2.

**Table 1:** Demographic and disease characterstics at the base line

| Demography | |
|---|---|
| Number of Patients | N=140 |
| Male/female n %) 100/40 | (71.43%/28.57%) |
| Age (years) | 37.6±10.86 |
| Weight (Kgs) | 60.5±8.43 |
| Disease characterstics at baseline | |
| Mean HBVDNA | Log 5.99± 1.116 IU/mL |
| Mean Serum ALT | 69.7 ±25.88 IU/L |
| HBeAg positive | N=140 (100%) |

**Table -2** HBeAg serocon version

| | Baseline | 40 weeks |
|---|---|---|
| HBeAg positive 140 | (100.0%) | 90 (64.29%) |
| HBeAg negative | 00 (00.0%) | 50 (35.71%) |

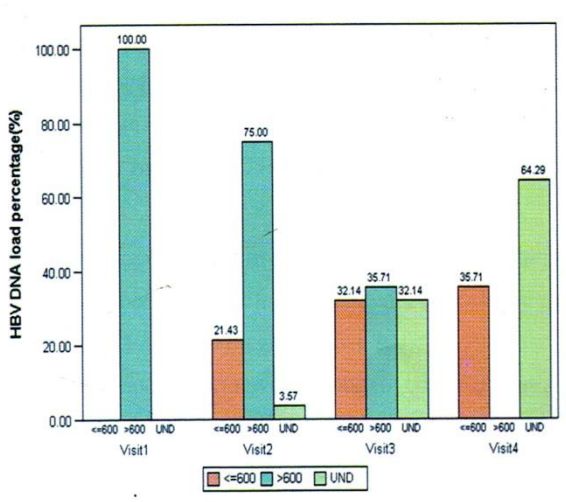


Figure 1: Bar graph for HBV DNA viral load undetectable (UND) ≤ 20 IU/mL

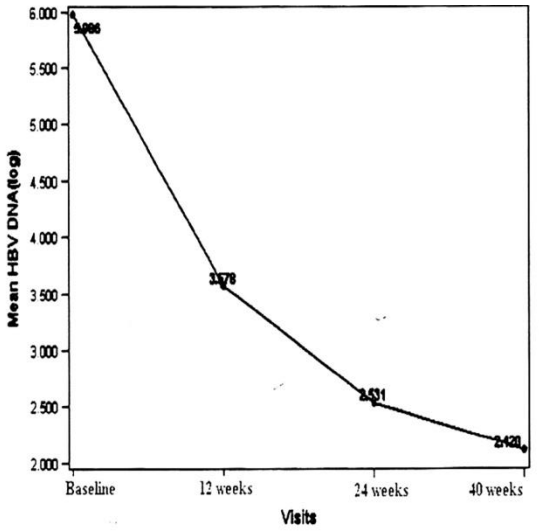


Figure 2: Changes in HBV-DNA (log) viral load from baseline to 40 week

## DISCUSSION

Although the efficacy of ETV to suppress the HBV DNA load have been demonstrated in various clinical trials there is limited data on its use in real clinical practice in India. This prospective, observational study assessed the efficacy of ETV in the routine clinical management of treatment naive CHB patients. Our study demonstrates that ETV is associated with significantly higher rates of serologic, viral, and biochemical improvement. Undetectable levels of HBV DNA by PCR assay were noted in 64.29% of patients by 40 weeks of treatment. Starting from the beginning of the study to its completion at 40 weeks ALT normalization was noted in 100% and HBeAg Serocon version in 35.71% patients Our results are in agreement with findings of chang et al[5] who showed in their study that a significantly greater number of patients on ETV achieved undetectable levels of HBV DNA than patients on lamivudine when monitored with PCR assay (67% vs.36%,p<0.001) and ALT levels (68% vs.60%).The limitation of our study were that safety parameters were not taken into consideration , data of the patients after 40 weeks of treatment was not available therefore further studies are recommended to evaluate rebound increase in viral DNA load, development of EVT resistance and long term safety of the drug. Our study cohort was small and patients had no other

co-morbid conditions or any concurrent drug therapy. Thus further studies evaluating the efficacy in such complex settings. We conclude that entecavir significantly improves viral biochemical and serological markers of HBeAg positive chronic hepatitis treatment naive patients who have not received nucleoside analogs for their condition.

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