ON TREATMENT EFFICACY OF ENTECAVIR IN TREATMENT NAÏVE CHRONIC HEPATITIS B PATIENTS

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Abstract

Background: Worldwide 250 million people are suffering from Hepatitis B Virus (HBV) infection. Treatment with antiviral drugs improve survival and quality of life by preventing disease progression and Hepatocellular Carcinoma (HCC). Indications for antiviral treatment primarily based on serum HBV DNA, Alanine Aminotransaminase (ALT) and severity of liver disease. Entecavir is one of the potent antiviral drug against hepatitis B virus. This study has been conducted to evaluate the efficacy of entecavir in both Hepatitis Be Antigen (HBeAg) positive and HBeAg negative treatment naïve Bangladeshi patients. **Materials and methods:** A total 205 patients were enrolled in this study from 2010-2014 in outpatients department of Hepatology in Chattogram Medical College Hospital. All patients got Entecavir 0.5 mg daily and followed at 12 weeks, 24 weeks & 52 weeks of the treatment by ALT, HBsAg, HBeAg and HBV DNA. 55 patients lost during follow-up and 150 patients completed 52 weeks treatment and finally evaluated. **Results:** The mean HBV DNA at baseline was 26.4 x 10^9 ± 7.4 x 10^9 copies / ml which was decreased to 2.2 x 10^6 ± 1.4 x 10^5 copies/ml at the end of 52 weeks which was statistically significant. At 52 weeks 118 (78%) CHB patient became HBV DNA negative. The mean ALT level before treatment were 96.1 ± 70.9 U/L which were 39.7 ± 11.98 U/L at the end of 52 weeks. At 52 weeks of treatment 78 (71.5%) became HBeAg negative. **Conclusion:** Entecavir significantly suppress HBV DNA level as well as normalization of aminotransfersae level. It has significant influences on HBeAg negativity in HBeAg positive chronic hepatitis B patients.

Key words
Chronic hepatitis B; Entecavir; (ETV) HBV DNA.

Introduction

Chronic Hepatitis B virus (HBV) infection affects an estimated 250 million people worldwide with a million death annually[1]. Sequelae of chronically infected patients are at increased risk of liver-related morbidity, namely, cirrhosis and Hepatocellular Carcinoma (HCC) in one third patients. Though remaining two third asymptomatic are at an increased risk of liver damage. Loss of Hepatitis B surface Antigen (HBsAg) and development of Anti HBS which are the hallmarks of eradication HBV infection, is usually not possible with the currently available therapies. Fatal liver disease-related events, such as cirrhosis, decompensation and HCC can be prevented by reduction of viraemia or DNA negativity[2].

Indication of treatment with antiviral drugs includes all patients with HBeAg-positive or -negative chronic hepatitis B, defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, Patients with compensated or decompensated cirrhosis with any detectable HBV DNA level and regardless of ALT levels, Patients with HBV DNA >20,000 IU/ml and ALT >2xULN regardless of the degree of fibrosis.

Treatment of HBV has greatly improved with the availability of Nucleoside / Nucleotide Analogues (NAs) such as Lamivudine (LAM) Adefovir Dipivoxil (ADV) Tenofovir Disproxil Fumarate (TDF) Entecavir (ETV) Telbivudine (LdT) and Tenofovir Alafinamide (TAF). Due to their high efficacy and low risk of antiviral resistance ETV and TDF are recommended as first line treatment.

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Submitted on : 05.01.2019
Accepted on : 24.06.2019

Entecavir is a potent nucleoside analogue with high genetic barrier to resistance. In one study patient on Entecavir monotherapy had more viral clearance by 12 weeks than patients receiving adefovir monotherapy[3]. Treatment of CHB has greatly improved after the discovery of NAs. LAM and ADV therapies though had fine initial response in clinical parameters in CHB but failed to obtain any benefit in long run[4]. ETV & TDF shows significant improvement in the form of Clinical, Biochemical & Virological response[4].

ETV therapy has shown improvement in both clinical and biochemical parameters during the median duration of 03-12 months[5-10]. Several studies conducted earlier, have confirmed that ETV therapy with high virological supression and minimal occurrence of Virological Break Through (VBT)[6,7,10-13].

This study was undertaken to see the on treatment efficacy of Entecavir on treatment naïve CHB patients.

Materials and methods

This prospective study was done at outpatient department of Hepatology of Chattogram Medical College Hospital from July 2010 to June 2014 after informed written consent from the patient.

Inclusion criteria

i) Age > 18 years

ii) HBsAg positive for >6 months

iii) Persistently or intermittently elevated ALT and HBV DNA > 10^5 copies /ml in HBeAg positive and >10^4 copies /ml in HBeAg-negative patients

iv) Treatment naïve (No previous NAs or Interferon) patient.

Exclusion criteria

i) Patient with Hepatitis C virus (HCV) co-infection, presence of HCC and active alcohol abuse over the past three months.

Initially, 205 treatment naïve CHB patients were enrolled in this study. ETV 0.5 mg daily was given in each patient. 55 patients were lost during the period of follow up. Final analysis was done on 150 patients who completed and were compliant for 52 weeks of the drug administration.

Biochemical, serological and virological response were evaluated at 12 weeks, 24 weeks and 52 weeks by ALT, HBsAg, HBeAg and HBV DNA. Quantitative polymerase chain reaction (qpcr) were done for HBV DNA detection (ABI 7500 Fast Dx real time PCR Instrument, Life Technology, USA). HBsAg, HBeAg were tested by commercially available immuneassay kits.

All the data was collected and recorded systematically in questionnaire. Results on continuous measurements are presented on mean ± SD and categorical measurements are presented in number (%). Chi-squared test and student's t-test were used to analyze and p value <0.05 was taken as significant.

Results

The mean age of 150 patients with chronic hepatitis B included in this study was of 30.6±10.39 years with male preponderance by more than five times.

Table I : Baseline characteristics of the study population (n=150)

Age (in years)	Number of patient	Percentage %
18-20	25	16.7%
21-30	69	46.0%
31-40	34	22.6%
>40	22	14.7%
Sex		
Male	125	83.33%
Female	25	16.67%
ALT (U/L)	96.1 ± 70.9 U/L	
HBeAg +ve	109	
HBeAg -ve	41	
HBV DNA	26.4 x 10^9 ± 7.4 x 10^9 copies /ml	

Table II : Serological response after 52 weeks of treatment (n=109)

	HBeAg		
	At 12 weeks n (%)	At 24 weeks n (%)	At 52 wks n (%)
Negative	0 (0%)	51 (46.78%)	78 (71.5)

Table II shows 71.5% patient became HBeAg negative at 52 weeks of treatment.

Table III : ALT and HBV DNA response of the study population at 52 weeks of treatment (n=150)

	Before treatment (n=150)		At 52 weeks of treatment (n=150)		p value
	Mean	±SD	Mean	±SD	
ALT	96.1	± 70.9	39.7	±11.98	0.001
HBV-DNA	26.4 x10^9	±7.4x10^9	2.2x10^6	±1.4x10^5	0.001

p value from Paired 't' test

The mean ALT was 96.1±70.9 in before treatment and 39.7 ±11.98 in after treatment. The mean HBV DNA was $26.4´10^9 \pm 7.4´10^9$ in before treatment and $2.2´10^6 \pm 1.4´10^5$ after 52 weeks of treatment. The difference was statistically significant ($p<0.05$) between before and after treatment (Table III).

Table IV : HBV DNA at 12 wks, 24 wks and 52 wks of treatment (n=150)

	HBV DNA					
	At 12 wks		At 24 wks		At 52 wks	
	n	%	n	%	n	%
Detectable	136	89.71	32	21.3	32	21.3
Undetectable	14	10.29	118	78.7	118	78.7

Table IV shows HBV DNA was undetectable in 78.7% CHB patient after 52 weeks of treatment.

Discussion

This single centre prospective study evaluated the efficacy of ETV in treatment naïve CHB patient. Base line characteristics shows in table-1, 125 (83%) male with mean age of 36±10.39. Male predominance may be due to more access of male patient to health care system. 109 (73%) patients are HBeAg positive, HBeAg positive patients are more younger than HBeAg negative patient. The base line HBV DNA level in the HBeAg positive patient were higher than that in the HBeAg negative patients. These findings are consistent with the natural history of CHB infection.

Undetectable levels of HBV DNA by PCR assay were noted in 78.7 % of patients by 52 weeks of treatment. This findings are consistent with the findings of Ismail et al. who showed in their study 84% virological response after 6 months of treatment with ETV[14]. In this study early virological response was 10.29%.

Out of 109 HBeAg positive patients at base line, 51 patients (46.78%) became HBeAg negative at the end of 24 weeks of treatment and a total of 78 patients (71.55%) became HBeAg negative at the end of 52 weeks of treatment. This findings is higher than other studies[15].

ALT was normal in all patients after 52 weeks of treatment. These findings are consistent with the findings of Chang et al who showed in their study that a significantly greater number of patients on ETV achieved undetectable levels of HBV DNA and normalization ALT levels[16].

None of the patient loss HBsAg during 52 weeks treatment.

Limitations

The limitations of the study are data of the patients after 52 weeks of treatment was not available, the sample size was small. Another limitation of this study Anti HBe was not seen.

Conclusion

Entecavir significantly suppress HBV DNA level as well as normalization of aminotransfersae level. It has significant influences on HBeAg negativity in HBeAg positive chronic hepatitis B patients. But this virological and serological response are lost in most CHB patient after stopping antiviral drugs. So, long term treatment with large sample size is necessary see the efficacy of ETV in CHB patient in Bangladesh.

Recommendation

Multicenter with large size study is recommended.

Acknowledgement

We express our heartiest gratitude to the staff of Hepatology Department of CMCH.

Contribution of authors

AKR- Conception, design, acquisition of data, drafting and final approval.
MIH- Analysis, critical revision and final approval.

Disclosure

All the authors declared no competing interest.

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