

# Efficacy and Safety of Entecavir 0.5 mg in Treating Naive Chronic Hepatitis B Virus Patients in Egypt: Five Years of Real Life Experience

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## Abstract

**Background:** The aim of the study was to evaluate the efficacy and safety of *entecavir* (ETV) among chronic hepatitis B (CHB) nucleos(t)ide-naïve Egyptian patients.

**Methods:** Forty-eight CHB patients on ETV were included. Males comprised 83.3% (40 cases), while females comprised 16.7% (eight cases). Minimum age was 19 years, while maximum age was 64 years. Hepatitis B envelope antigen (HBeAg)-negative cases were 60.4%. HBeAg-positive cases were 39.6%. Factors including sex, positive HBeAg, baseline hepatitis B virus (HBV) DNA level, baseline alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were evaluated in terms of their predictive role in treatment response, which was defined as a serum HBV DNA decrease of < 10 IU/mL.

**Results:** Mean age of patients was 38.2 years; males were 83.3% and females were 16.7%. HBeAg-negative cases were 60.4%, while HBeAg-positive cases were 39.6%. Mean baseline DNA level was  $44 \times 10^6$  IU/mL. Ultrasound results showed 14 cases had hepatomegaly, 10 cases had bright liver, seven cases had coarse liver, and eight cases had cirrhosis. Of the cases, 45.8% showed a negative PCR after the first 6 months of therapy to reach 64.6% by the end of the first year. HBV DNA undetectability reached 91.3% and 100% after 4 and 5 years, respectively for those who completed the study period. ALT reduction started after 6 months of treatment and reached 53.37% after 5 years. Similarly AST showed the same pattern of decline and

reached 54.37% after 5 years. Only two cases achieved HBeAg seroconversion. Three patients experienced virological breakthrough and the three cases shared similar characteristics of being less than 40 years, with baseline HBV DNA of  $\geq 10^5$  IU/mL and positive HBeAg. None of the cases showed hepatitis B surface antigen (HBsAg) seroconversion.

**Conclusion:** ETV proved to have a potent antiviral *efficacy and safety* in nucleoside/tide-naïve Egyptian patients. Rate of HBV DNA undetectability was higher in patients above 40 years of age and in patients who initially had a low viral load. ETV was well tolerated during the treatment period with a good overall *safety* profile.

**Keywords:** Hepatitis B; Entecavir; Egypt

## Introduction

The prevalence of chronic hepatitis B virus (HBV) infection is approximately 800,000 to 1.4 million people in the United States and 350 million worldwide. Serious morbidity occurs in approximately 15-25% of people with chronic HBV infection, including liver damage or liver failure, cirrhosis, or liver cancer, and HBV causes approximately 620,000 deaths annually worldwide [1]. Viral replication is now recognized as the key driver of liver injury and disease progression, and thus the primary aim of treatment for chronic HBV infection is long-term suppression of HBV replication to undetectable levels [2, 3]. Therefore, the goal of therapy for chronic hepatitis B (CHB) patients is to delay or prevent progression of liver disease by suppressing long-term HBV DNA replication [4]. Antiviral drugs available for HBV treatment include interferon-alpha (INF- $\alpha$ ) and nucleos(t)ide analogue (NA) polymerase inhibitors (lamivudine (LAM), adefovir, entecavir (ETV), telbivudine and tenofovir). Treatments include individualized single-agent or combination therapies. Evidence-based medicine has demonstrated that effective antiviral treatment of CHB reduced the risk of long-term complications and improved patient survival [4, 5]. LAM was the first nucleoside analog inhibitor to be approved for treatment of CHB infection and has been used widely in the treatment of CHB patients. However, a major shortcoming of LAM-based therapies is the development of

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drug-resistant strains that develop with increasing frequency with treatment duration [6]. The rate of LAM resistance is 24% after 1 year and approximately 70% after 5 years. Furthermore, LAM resistance leads to the attenuation of HBV suppression and even causes hepatitis flare ups, hepatic decompensation and increased mortality rates, thereby posing a serious clinical challenge [7].

ETV is a cyclopentyl guanosine analogue, and a potent and selective inhibitor of HBV replication *in vitro* [8]; its efficacy has been demonstrated in both patients with Hepatitis B envelope antigen (HBeAg)-positive and patients with HBeAg-negative chronic HBV infection. Treatment with the potent antiviral agent like ETV for periods ranging from 48 weeks to 3 years has shown superior virologic, histologic, and biochemical outcomes in nucleoside-naïve patients, with minimal emergence of resistance [9]. Compared with LAM, 1 year of treatment with ETV 0.5 mg daily in nucleoside-naïve patients with HBeAg-positive or HBeAg-negative chronic HBV infection was associated with significantly improved liver histology and virologic and biochemical endpoints [10].

Although proven international efficacy, yet efficacy and safety profile of widespread use of ETV (Baraclude 0.5 mg, BMS) was not evaluated in Egypt. The study aimed at evaluating the efficacy and safety of ETV among CHB nucleos(t)ide-naïve Egyptian patients.

## Patients and Methods

The study evaluated 48 nucleoside-naïve chronic HBV patients who were treated with ETV 0.5 mg (Baraclude 0.5 mg, Bristol Myers Squibb, BMS) monotherapy for a period of 1 - 5 years. Recruited patients were selected from patients regularly attending a specialized HBV outpatient clinic on twice weekly basis at National Hepatology and Tropical Medicine Research Institute (NHTMRI), Cairo. Recruitment started in June 2009 and ended in June 2014. The medication was given to the patients as part of their routine medical care they are given at the clinic with no sponsorship whatsoever from the producing pharmaceutical company. A pre-designed pretested sheet was used to record clinical information from each recruited patient. Part of the data was obtained from patients' files, which included all pre-enrolment data collected before the recruitment of patients. Other data were actively collected from each recruited patient during the follow-up visits. Basic data such as age, sex, and residency were recorded. All patients were over 18 years of age, positive for hepatitis B surface antigen (HBsAg) for at least 6 months, showing persistent elevation of transaminases for 6 months and both HBeAg-positive and HBeAg-negative patients were included. Exclusion criteria included co-infection with hepatitis C, D viruses, evidence of liver decompensation or hepatocellular carcinoma, history of alcohol or drug abuse within 1 year prior to enrollment in the study, other possible causes of chronic liver damage, or previous treatment for CHB. Females who were planning for pregnancy or nursing were also excluded. The study protocol conformed to the ethical guidelines and was approved by the Research Ethics Committee of the General Organization for

**Table 1.** Patients and Ultrasound Results

	Frequency	Percent
Sex	8	16.7%
Female	40	83.3%
Male		
HBeAg-0		
Negative	29	60.4%
Positive	19	39.6%
HCV Ab		
Negative	48	100%
Positive	0	0.0%
US-0		
Bright liver	10	20.8%
Cirrhosis	8	16.7%
Coarse liver	7	14.6%
Hepatomegaly	14	29.2%
Normal	9	18.8%

Teaching Hospitals and Institutes, Cairo. Among 60 naïve patients treated with ETV 0.5 mg/day, 12 were excluded because of poor compliance to treatment or interrupted treatment courses. A total of 48 patients were eligible for this analysis. All patients were subjected to pre-enrolment investigations in the form of HBsAg, HBeAg, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, complete blood picture (CBC), alpha-fetoprotein (AFP) testing, serum creatinine, serum albumin, hepatitis C virus antibody (HCV Ab) testing, hepatitis delta antibody testing, quantitative HBV-DNA assays and abdominal ultrasound. The diagnosis of cirrhosis was based on ultrasound examinations.

All patients were educated individually about the nature of the disease, the treatment regimen and the importance of adhering to the medication. Also were instructed that the drug should be administered on an empty stomach (at least 2 h before or after a meal and 2 h before the next meal).

The patients were monitored on a monthly basis to supply the medication, follow-up on the treatment compliance and to ensure there were no complications or side effects. Every 3 months, our patients were subjected to investigations for ALT, AST, total bilirubin, CBC and serum creatinine and every 6 months to HBeAg, hepatitis B envelope antibody (HBeAb), ALT, AST, total bilirubin, CBC, AFP, serum creatinine in addition to quantitative HBV-DNA testing and abdominal ultrasound. All patients were subjected to HBsAg and hepatitis B surface antibody (HBsAb) testing annually during treatment. The patients were carefully examined at each follow-up visit and asked to report any incidence of adverse events.

## Statistical methods

Statistical Package for Social Science (SPSS) program version 17.0 was used for data analysis. Mean and standard deviation

**Table 2.** Percent Change in Levels of ALT, AST and Serum Creatinine Over Study Period as Compared to Baselines Among Study Subjects

	Mean	Standard deviation	Minimum	Maximum
ALT AT 6 months (n = 48)	-43.2	± 36.7	-90.7	109.76
ALT at 12 months (n = 48)	-48.1	± 28.7	-93.87	12.2
ALT at 24 months (n = 40)	-51.9	± 35.7	-94.71	62.96
ALT at 36 months (n = 31)	-52.0	± 26.5	-92.47	27.69
ALT at 4 years (n = 24)	-56.2	± 23.8	-90.91	21.95
ALT at 5 years (n = 16)	-53.4	± 28.4	-94.29	18
AST at 6 months (n = 48)	-36.2	± 29.4	-89.7	27.9
AST at 12 months (n = 48)	-44.6	± 27.8	-89.4	27.59
AST at 24 months (n = 40)	-49.1	± 30.4	-88.74	37.04
AST at 5 years (n = 16)	-54.4	± 19.2	-84.96	-13.95
Serum creatinine at 12 months (N = 48)	41.86	± 49.9	-27.27	175
Serum creatinine at 5 years (N = 16)	34.08	± 41.2	-20	116.67

ALT showed 43.2% reduction on average comparing its level from baseline to 6 months and 48.14% reduction after 1 year of treatment from baseline and reached 53.37% after 5 years. AST showed 36.15% reduction on average comparing its level from baseline to 6 months and 44.57% reduction after 1 year of treatment from baseline and reached 54.37% after 5 years. Serum creatinine levels showed an increase by 41.85% on average after 1 year of treatment versus 34.07% after 5 years of treatment.

(SD) and median and interquartile range (IQR) were estimates of quantitative data while frequency and percentage were estimates of qualitative data. Student's *t*-test was used to compare the responses over time.

## Results

The study included 48 patients, where males comprised 83.3% (40 cases) and females comprised 16.7% (eight cases). The mean age of our patients was 38.2 years, where the minimum age was 19 years and the maximum age was 64 years. HBeAg-negative cases were 26 (60.4%), while HBeAg-positive cases were 19 (39.6%) (Table 1).

Ultrasound results showed that 14 cases (29.2%) had hepatomegaly, 10 cases (20.8%) had bright liver, seven cases (14.6%) had coarse liver, and eight cases (16.7%) had liver cirrhosis (Table 1).

The mean starting ALT level is 98.5 (32 - 385), while the mean for AST is 68.3 (21 - 239) (Table 2).

Results proved that HBV DNA undetectability started from the first 6 months of treatment, where 22 cases showed a negative PCR after the first 6 months of therapy. Nine more cases had a negative PCR after 1 year of treatment to be a total of 31 cases out of 48 (64.6%) by the end of the first year. HBV DNA undetectability reached 91.3% and 100% after 4 and 5 years, respectively (Table 3).

ALT showed 43.2% reduction on average comparing its level from baseline to 6 months and 48.14% reduction after 1 year of treatment from baseline and reached 53.37% after 5 years. AST showed 36.15% reduction on average comparing its level from baseline to 6 months and 44.57% reduction after 1 year of treatment from baseline and reached 54.37% after 5 years of continuous (Table 4).

Only two cases (4.16%) out of 19 cases (39.6%) managed to achieve HBeAg seroconversion. The first case achieved seroconversion after 36 months of treatment. The second case achieved seroconversion at 12 months of treatment.

Three patients (6.25%) experienced virological breakthrough and the three cases shared similar characteristics of being less than 40 years of age, with a starting HBV DNA of  $\geq 10^5$  IU/mL and positive HBeAg.

Serum creatinine levels showed an increase by 41.85% on average after 1 year of treatment versus 34.07% after 5 years of treatment and both results showed statistical significance (Table 5).

Table 3 shows the correlation between age (classified as below or above 40 years of age) and different parameters as HBV DNA, ALT levels and serum creatinine. HBV DNA levels were found significantly less in those above 40 years of age. This finding was found statistically significant at baseline and at 24 months of therapy. None of our cases cleared HBsAg during their treatment course.

## Discussion

The present cohort study represents to our knowledge the first study to assess the efficacy and safety of ETV among Egyptian patients. Egypt although classified by the World Health Organization (WHO) to be an area of intermediate prevalence of 4-8%, yet CHB is still considered a major health problem due to the long duration of treatment, associated co-morbidities and the potential high cost of therapy. HBV chronically infects more than 400 million people worldwide. Major breakthroughs have been achieved in diagnosis and treatment of this virus [9, 11]. Ultimately, the treatment for CHB aims to suppress HBV replication, relieve inflammation, prevent fibrosis and hepatocellular

**Table 3.** Relation of Age Group to Different Parameters at Different Intervals of Study Period

Parameter	Age	Mean	Standard deviation	Significance
ALT baseline	< 40 years	82.4	± 44.8	0.187
	40+	113.2	± 101.6	
DNA baseline	< 40 years	80,063,074	± 122,898,706	0.009*
	40+	11,774,394	± 25,576,875	
Serum creatinine baseline	< 40 years	0.7	± 0.2	0.016*
	40+	0.9	± 0.2	
DNA at 12 months	< 40 years	15,926	± 53,180	0.149
	40+	317	± 1,475	
Serum creatinine at 12 months	< 40 years	0.9	± 0.2	0.02*
	40+	1.1	± 0.3	
ALT at 12 months	< 40 years	33.1	± 11.1	0.159
	40+	39.2	± 17.2	
ALT at 24 months	< 40 years	38.3	± 17.7	0.139
	40+	30.5	± 15.1	
Serum creatinine at 24 months	< 40 years	0.9	± 0.2	0.463
	40+	1.0	± 0.2	
DNA at 24 months	< 40 years	2,410	± 5,534	0.047*
	40+	1.2	± 5.8	
DNA at 5 years	< 40 years	0.0	-	-
	40+	0.0	-	
ALT at 5 years	< 40 years	37.3	± 15.4	0.064
	40+	27.3	± 5.5	
Serum creatinine at 5 years	< 40 years	0.8	± 0.4	0.05*
	40+	1.1	± 0.2	

\*DNA levels were found significantly higher among age group below 40 at baseline and at 24 months of treatment (P = 0.009 and 0.047, respectively). On the contrary, age group above 40 years showed statistically significant higher serum creatinine at baseline and at 12 months of treatment (P = 0.016 and 0.02, respectively).

carcinoma (HCC), and increase the survival rate [12, 13]. However, chronic HBV infection is not completely eradicated due to persistence of covalently closed circular DNA (cccDNA) of nucleus in the infected hepatocytes, and this can result in HBV reactivation [14-16]. So it is important to decrease and maintain serum HBV DNA level to the undetectable level as the actual purpose of treatment for CHB [17-19]. ETV is a cyclopentyl guanosine analogue that undergoes intracellular phosphorylation to its active 5-triphosphate metabolite. This form competes with the natural substrate deoxyguanosine triphosphate to inhibit HBV DNA polymerase, which is essential for viral replication. Hence, the drug is considered a potent and selective inhibitor of HBV replication *in vitro* [20]. The rates of histologic improvement, virologic response, and normalization of ALT levels were significantly higher with ETV than with LAM and adefovir dipivoxil (ADV) [21]. ETV is considered effective in the suppression of HBV replication, inducing HBeAg seroclearance, and reduces cirrhosis and HCC development [22].

ETV in general has a good safety profile and tolerability [23]. Most of our patients did not experience serious adverse

event during the study time while receiving ETV treatment. Only few reports on mild dizziness, transient abdominal discomfort at the beginning of the treatment course. None of our patients stopped medication because of adverse events. One patient 31 years old experienced the development of multiple pancreatic cysts, which were not preceded by acute pancreatitis, ERCP maneuver or any other related cofactors. The patient experienced reaccumulation of the cysts after drainage and repeated cytology examinations proved no malignancy. No direct correlation with the drug could be proved. Very few reports in literature were found regarding the association of ETV with acute pancreatitis. Kim and colleagues stated the possibility of adverse drug reactions (ADRs) related to ETV therapy in patients with advanced cirrhosis including lactic acidosis, myalgia, neuropathy, azotemia, hypophosphatemia, muscular weakness, and pancreatitis, as well as immune-mediated responses [24]. Moreover, in another study, a possible role of antiretroviral therapy with ETV was suggested in cases with hyperlipidemic pancreatitis [25].

In our study, all patients were fulfilling the criteria of eli-

**Table 4.** ALT and AST Change Reduction Over Study Period

	N	Mean	Standard deviation	Minimum	Maximum
Per_changeALT0_6	48	-43.2	36.7	-90.7	109.76
Per_changeALT0_12	48	-48.1	28.7	-93.87	12.2
Per_changeALT0_24	40	-51.9	35.7	-94.71	62.96
Per_changeALT0_36	31	-52.0	26.5	-92.47	27.69
Per_changeALT0_4 years	24	-56.2	23.8	-90.91	21.95
Per_changeALT0_5 years	16	-53.4	28.4	-94.29	18
Per_changeAST0_6	48	-36.2	29.4	-89.7	27.9
Per_changeAST0_12	48	-44.6	27.8	-89.4	27.59
Per_changeAST0_24	40	-49.1	30.4	-88.74	37.04
Per_changeAST0_5 years	16	-54.4	19.2	-84.96	-13.95

ALT showed 43.2% reduction on average comparing its level from baseline to 6 months and 48.14% reduction after 1 year of treatment from baseline and reached 53.37% after 5 years. AST showed 36.15% reduction on average comparing its level from baseline to 6 months and 44.57% reduction after 1 year of treatment from baseline and reached 54.37% after 5 years.

gibility to treatment with HBV DNA > 2,000 with successive persistent elevation of transaminases. According to EASL practice guidelines 2012, a liver biopsy is not required in patients with clinical evidence of cirrhosis or in those in whom treatment is indicated irrespective of the grade of activity or the stage of fibrosis.

Abdominal ultrasound was repeatedly done every 6 months during our treatment course but results were almost the same with no significant change observed.

ETV treatment was associated with significant improvement in the biochemical profile of the patients during the study period. ALT showed 43.2% reduction on average comparing its level from baseline to 6 months and 48.14% reduction after 1 year of treatment from baseline and reached 53.37% after 5 years. Similarly AST levels showed significant reduction, which reached 54.37% after 5 years of continuous treatment. Shin and colleagues in 2015 found similar results in their study that detected that ETV improves liver function and also non-invasive fibrosis markers in patients with HBV-associated cirrhosis [26].

ETV as a potent and safe agent leading to continuous viral suppression proved to be safe and well tolerated therapy [27]. Our results also showed that HBV DNA undetectability started from the first 6 months of treatment, where 22 cases showed a negative PCR after the first 6 months of therapy. Nine more cases had a negative PCR after 1 year of treatment to be a total of 31 cases by the end of the first year.

One of the aims of the study was to determine whether continuous ETV therapy is feasible to achieve HBeAg seroconversion. Only two cases (4.16%) managed to achieve HBeAg seroconversion. The first case had a starting PCR of  $95 \times 10^3$  IU/

mL and achieved early HBV DNA undetectability after the first 3 months of treatment and HBeAg seroconversion at 36 months of treatment. The second case had a higher starting PCR of  $20 \times 10^6$  IU/mL, and achieved both HBV DNA undetectability and HBeAg seroconversion after 12 months of treatment. None of the cases who failed to clear HBV DNA after 1 year of treatment achieved HBeAg seroconversion. Similarly, in an earlier study prolonged ETV therapy was not found very effective in achieving HBeAg seroconversion in treatment-naive CHB patients with a partial virological response. In their study partial virological response was defined as detectable HBV DNA (> 116 copies/mL) at year one [28]. The two cases received consolidation treatment for 1 year after confirming HBeAg seroconversion on two different occasions 3 months apart.

The high potency of ETV is mainly attributed to its structural formula and mechanism of action which requires the occurrence of both LAM mutations and a specific "signature" ETV mutation, therefore, ETV is associated with emergence of minimal resistance in the long-term treatment of nucleoside-naive patients [29]. In our study, three patients (6.25%) experienced virological breakthrough and the three cases shared similar characteristics of being less than 40 years of age, with a starting HBV DNA of  $\geq 10^5$  IU/mL and HBeAg-positive virological breakthrough started after 2 years of continuous treatment in one case and after 3 years in two cases. Tenofovir was only launched in Egypt in 2012 so for the first two cases, ADV 10 mg was added to ongoing ETV 0.5 mg and the third case received tenofovir disoproxil fumarate (TDF) 300 mg.

These data support the conclusion that ETV 0.5 mg naive patients leads to potent suppression of HBV DNA, normalization of ALT, long-term ETV therapy for up to 5 years

**Table 5.** Serum Creatinine Levels Showed an Increase by 41.85% on Average After 1 Year of Treatment Versus 34.07% After 5 Years of Treatment

	N	Mean	Standard deviation	Minimum	Maximum
Per_changeSCreat0_12 months	48	41.86	49.87	-27.27	175
Per_changeSCreat0_5 years	16	34.08	41.37	-20	116.67

in our study was generally well tolerated, including those with cirrhosis at baseline. Substantially patients demonstrated biochemical improvement regarding normalization of both ALT and AST levels after few months of treatment and during long-term follow-up. The safety profile, potent suppression of HBV replication, and low potential for antiviral drug resistance in nucleoside-naïve patients make long-term treatment of CHB with ETV monotherapy is greatly favored if compared to other lines of treatment. Closer follow-up of is required in HBeAg-positive cases with high baseline levels.

## Abbreviations

HBV: hepatitis B virus; HCC: hepatocellular carcinoma; CHB: chronic hepatitis B; ALT: alanine aminotransferase; AST: aspartate aminotransferase; NA: nucleos(t)ide analogue; LAM: lamivudine; ADV: adefovir dipivoxil; ETV: entecavir; CBC: complete blood picture; cccDNA: covalently closed circular DNA; TDF: tenofovir disoproxil fumarate; BMS: Bristol-Myers Squibb; NHTMRI: National Hepatology and Tropical Medicine Research Institute

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