EJMI

DOI: 10.14744/ejmi.2019.70738
EJMI 2019;3(4):322–326

Research Article

Assessment of Efficacy, Reliability, Side Effects and Patient Compliance of Entecavir in Turkish Patients with Nukleos(t)ide Analogues Naive Chronic Hepatitis B

Mustafa Karaagac, Nevzat Aksoy, Kemal Kutoglu, Nurten Arican, Semih Kalyon, Necati Yenice

Department of Internal Medicine, Health Sciences University, Okmeydani Training and Research Hospital, Istanbul, Turkey

Abstract

Objectives: This study aimed to assess the entecavir (ENT) in Turkish patients with nukleos(t)ide analogues (NA) naive chronic hepatitis B (CHB).

Methods: The data in this study were collected retrospectively. The rates of compliance, biological, virological, and serological responses, and drug resistance and the frequency of ENT-related side effects were determined.

Results: A total of 40 patients were enrolled in this study. The rates of virological response, biochemical response in HBeAg (-) patients were 100% and 96.6%, respectively. There was no HBsAg loss in HBeAg (-) patients. The rates of virological response, biochemical response, serological response, and HBsAg loss in HBeAg (+) patients were 100%, 90%, 70%, and 10% respectively. The rates of virological response and biochemical response in both HBeAg (-) and (+) patients were 100% and 95%, respectively. Complete response was detected in only one of 40 patients (2.5%) at the 96th week of treatment. The most ENT-related side effects were fatigue. Only two patients had mild renal impairment, whereas moderate or severe renal impairment was not detected.

Conclusion: The treatment of ENT can be safely used as an effective first-line drug in adult Turkish patients with NA-naive CHB. Patients should be followed up more closely in terms of renal function during treatment.

Keywords: chronic hepatitis B, entecavir, efficacy, naive

Cite This Article: *Karaagac M, Aksoy N, Kutoglu K, Arican N, Kalyon S, Yenice N. Assessment of Efficacy, Reliability, Side Effects and Patient Compliance of Entecavir in Turkish Patients with Nukleos(t)ide Analogues Naive Chronic Hepatitis B. EJMI 2019;3(4):322–326.*

Hepatitis B virus (HBV) infection is still one of the world's leading health problems.[1] More than 50 million people are infected with HBV every year, and more than 1 million deaths occur annually due to complications of chronic HBV infection.[2] Turkey is located in the moderate endemicity region concerning HBV infection.[3]

In order to prevent or minimize the occurrence of liver damage, the need to suppress HBV-DNA in the treatment of chronic hepatitis B (CHB) and its long-term necessity is emphasized.[4] Entecavir (ENT) is one of the drugs used for this purpose that is a cyclopentyl two deoxyguanosine nucleoside analog, approved in the United States in 2005 with high potency for profound and durable viral suppression and genetic barriers against resistance. The recommended dose of ENT for patients with nucleos(t)ide analogues (NA) naive CHB is 0.5 mg per day.[5, 6]

In this study, we evaluated the efficacy, reliability and side effects and patient compliance of ENT in Turkish patients with NA-naive CHB.

Address for correspondence: Mustafa Karaagac, MD. Okmeydanı Egitim ve Arastirma Hastanesi, Saglik Bilimleri Universitesi, Ic Hastaliklari Anabilim Dali, Istanbul, Turkey
Phone: +90 332 223 78 06 **E-mail:** mustafakaraagac55@hotmail.com

Submitted Date: April 08, 2019 **Accepted Date:** July 18, 2019 **Available Online Date:** September 30, 2019

Methods

This retrospective study was an internal medicine expertise thesis.

Ethical Approval

The study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of the University of Health Sciences Okmeydanı Training and Research Hospital.

Patients, Eligibility and Data Collection

In this study, we recruited 40 patients with NA-naive CHB who were beginning to treat with 0.5 mg ENT per day at the Gastroenterology Department of University of Health Sciences Okmeydanı Training and Research Hospital between May 2007 and July 2010. These patients included in our study were the first patients to use 0.5 mg ENT per day in our clinic, so they were followed up strictly, and their medical information was recorded carefully and regularly. All data were obtained by screening of patients files retrospectively.

Data on age, gender, alcohol consumption, smoking, body mass index (BMI), hypertension and diabetes mellitus as comorbidities, history of previous interferon (INF) treatment and ENT related side effects were recorded. Biochemical [aspartate transaminase (AST), alanine transaminase (ALT), Total Bilirubin (T.Bil), Direct Bilirubin (D. Bil), albumin, prothrombin time (PT), creatinine, alpha-fetoprotein (AFP)], serological [anti-HCV, anti-HDV, anti-HIV, HBV-DNA, HBsAg, anti-HBs, HBeAg, anti-HBe] and haematological [leukocyte (WBC), hemoglobin (Hb), thrombocyte (PLT)] parameters that had been achieved at the baseline and the control periods by the weeks 4, 12, 24 and the every 24th week of the treatment were noted. Definitions of biochemical, virological, serological responses and primary biochemical, primary virological, secondary virological unresponsiveness were determined as shown in Table 1.

Definitions about renal functions were determined according to changes in glomerular filtration rate (GFR) levels. GFR values were calculated using the Cockcroft-Gault formula ([(140-age) x body weight (kg)] / [serum creatinine (mg/dl) x 72] x [0.85, if female]), the method recommended by the National Kidney Foundation.[7] GFR levels of the patients were determined at baseline and during treatment. Renal functions were classified according to differences in GFR levels as intact, mildly impaired, moderately impaired and severely impaired (Table 1).

Statistical Analysis

Primary statistical analysis has included descriptive statistics. One-Sample Kolmogorov-Smirnov test was used for the normal distribution of the groups, and the non-parametric Mann-Whitney U test was used as the parametric test conditions could not be obtained in the comparison of the two groups. A p-value <0.05 was required for statistical significance. Statistical analysis was performed by using SPSS version 16 (SPSS Inc., Chicago, IL, USA).

Results

A total of 40 patients were enrolled in this study. There were 26 males and 14 females. The median age was 41years (19-67). The median time from initial diagnosis to ENT treatment was 6.1 years (1-14). Fifteen patients never used alcohol; 14 patients never smoked cigarettes. The me-

Table 1. Definitions of responses, unresponsiveness and renal impairment

Biochemical response	Normalization of ALT, continuous ALT normal values and presence of two normal ALT values followed at least one month after treatment responses
Virological response	Reducing HBV-DNA levels to less than 300 copies/ml
Serological response	Becoming negative of "e" antigen in patients with HBeAg (+)
Early response	Response status at the 4th, 12th and 24th weeks of the treatment
Complete response	Becoming normal ALT, HBsAg negative, anti-HBs positive, HBV-DNA negative, and HBeAg negative in patients with HBeAg (+)
Durable response	Continuation of respons during drug treatment
Primary biochemical unresponsiveness	ALT never fall to the normal levels
Primary virological unresponsiveness	<1log (10) decrease of HBV-DNA in the third month of treatment at responders
Secondary virological unresponsiveness	1log (10) or greater increase in viral titer compared to the lowest viral load level obtained during treatment at responders
Normal renal function	No reduction or minor reduction in GFR (0-10%)
Mild renal impairment	Slight reduction in GFR (11-20%)
Moderate renal impairment	Moderate reduction in GFR (21-30%)
Severe renal impairment	Significant reduction in GFR (>30%)

GFR: Glomerularm filtration rate.

dian BMI value was 26.2 kg/m^2 (20-36). Seven patients had comorbidities. The number of patients who received INF treatment for 12 months, less than 12 months and never used were 14, 3 and 23, respectively. At the beginning of ENT treatment, all patients were HBsAg (+) and antiHBs (-), twenty-one males and nine females were HBeAg (-), and the others were HBeAg (+). The median duration of treatment was 96,6 weeks (48-144), regardless of gender, and was 100,6 weeks (48-144) in males, and 89,1 weeks (48-144) in females. At the beginning of the treatment, median HBV-DNA level was 51.008.294,1 copies/ml (33.756-148.992.000), and HBV-DNA levels were 104-107 copies/ml in 52.5% and >107 copies/ml in 47.5% of patients (Table 2). At the 12th week of the treatment, the early biochemical response was obtained in all males and females, and this success was maintained after 12 weeks during the treatment.

The rates of virological response, biochemical response in HBeAg (-) patients were 100% and 96.6%, respectively. There was no HBsAg loss in HBeAg (-) patients. The rates of virological response, biochemical response, serological response, and HBsAg loss in HBeAg (+) patients were 100%, 90%, 70%, and 10% respectively. The rates of virological response and biochemical response in both HBeAg (-) and (+) patients were 100% and 95%, respectively.

Age (p=0.003), HBV-DNA (p=0.006), BMI (p=0.029) and PT (p=0.038) were statistically significant variables between

Table 2. The demographic and clinical parameters of patients.

Variable	Median±SD	Range
Number of patients	40	
F/M ratio	14/26	
Median age (years)	41.1±12.5	(19–67)
F/M ratio of HBsAg(+) patient	14/26	
F/M ratio of HBe Ag (-) patient	9/21	
F/M ratio of HBe Ag (+) patient	5/5	
Median		
Time from diagnosis to ENT treatment (years)	6.1±3.3	(1–14)
Treatment with ENT (weeks)	96.6±32.8	(48–144)
HBV-DNA (copies/ml)	51.008.294.1±58.053.301.1	(33.756–148.992.000)
AST (IU/L)	70.5±55.3	(32–261)
ALT (IU/L)	115.2±76.6	(71–357)
Total bilirubin (mg/dl)	0.7±0.3	(0.3–1.8)
Direct bilirubin (mg/dl)	0.2±0.1	(0.1–0.9)
İndirect bilirubin (mg/dl)	0.4±0.2	(0.1–0.9)
Albumin (g/dl)	4.1±0.4	(2.6–4.8)
PT (sec)	14.0±1.2	(11.7–20.2)
WBC (/mm^3)	5.971.2±1.864.6	(1.680–10.640)
Hb (g/dl)	14.0±1.6	(10.7–17.6)
PLT (10^3/mm^3)	190.962.5±84.596.8	(54.000–387.000)
Urea (mg/dl)	30.1±6.7	(17–44)
Creatinin (mg/dl)	0.93±0.16	(0.7–1.2)
GFR (ml/min)	110.4±19.6	(77–166)
BMI (kg/m^2)	26.2±4.04	(20–36)
No alcohol	15	
Ex-drinker	23	
Active drinker	2	
No smoking	14	
Ex-smoker	14	
Active smoker	12	
No Interferon	23	
Interferon <12months	3	
Interferon for 12 months	14	

F: Female; M: Male; ENT: Entecavir; GFR: Glomerular filtration rate; BMI: Body mass index.

HBeAg (+) and HBeAg (-) patients. AST (p=0.03) was the only statistically significant variable between serological responders and non-responders in HBeAg (+) patients.

Thirty-four patients at 24th weeks, three patients at 48th weeks, two patients at 72nd weeks and one patient at 120th weeks achieved a virological response. Alcohol consumption (p=0.005) and HBV-DNA levels (p=0.049) were statistically significant variables between early virological responders at 24th weeks and the others.

Complete response was detected in only one of 40 patients (2.5%) at the 96th week of treatment.

At the end of the study, primary or secondary virological unresponsiveness and ENT resistance were not determined in any patient, and the durable response was observed in all of our patients.

ENT-related side effects were detected in 14 patients (35%). All reported adverse events occurred during the first two weeks of treatment, and none of them were severe. The reported side effects were fatigue (22.5%), headache (10%), myalgia (10%), dizziness (7.5%), abdominal pain (5%), runny nose (2.5%), cough (2.5%), diarrhea (2.5%), and insomnia (2.5%), respectively. Elevation of ALT levels compared to baseline was detected in 1 patient, and thrombocytopenia was detected in 4 patients. All patients well-tolerated the treatment, and none of the patients left the drug.

The median baseline GFR level was 110.4 ml/min (77-166). GFR was decreased in 17 patients due to treatment. However, only two patients had mild renal impairment, whereas moderate or severe renal impairment was not detected. In conclusion, the rate of treatment-related renal impairment was determined as 5% in 40 patients included in the study. Age (p=0.029) was the only statistically significant variable between the patients with treatment-related renal impairment and the others.

Discussion

This retrospective study was an internal medicine expertise thesis. We evaluated the efficacy, reliability and side effects and patient compliance of 0.5 mg per day ENT treatment in Turkish patients with nukleos(t)ide analogues naive CHB. Early biochemical response was obtained in all males and females, and this success was durable. The rates of virological response, biochemical response, and serological response were very high. Alcohol consumption and high HBV-DNA levels were associated with delayed virological response. Primary or secondary virological unresponsiveness and ENT resistance were not determined in any patient. All ENT-related side effects occurred during the first two weeks of treatment, and none of them were severe. No moderate or severe renal impairment was detected; only two patients had mild renal impairment. All patients well-tolerated the treatment, and none of the patients left the drug.

The results of our study in patients with HBeAg (+) and HBeAg (-) were consistent with data in the literature.[8–11] Besides, in this study, the number of patients with HBeAg (-) was higher than that of HBeAg (+). This may be explained by the fact that our country is located in the middle endemic region for HBV infections and the infection is acquired in early childhood, especially by the horizontal path.

Sherman at al.[12] demonstrated that treatment responses and early access to goals were associated with basal HBV-DNA levels. Although the treatment unresponsiveness was not detected and usually early complete virological response was obtained in our study, six patients had a complete virological response more than 24 weeks later. We found that alcohol consumption and high HBV-DNA levels were associated with delayed virological response. It is possible to reach treatment targets in patients with high basal HBV-DNA levels, but, it should be kept in mind that this situation will occur later and prevention of alcohol consumption will facilitate the achievement of treatment goals.

In many studies with NA-naive CHB patients, the cumulative probability ratios for ENT resistance were calculated and in the 1st year, 2nd year, 3rd year, 4th year and 5th year this rate was expected as 0.2%, 0.5%, 1.2%, 1.2%, and 1.2%, respectively.[8, 13, 14] No primary or secondary unresponsiveness and ENT resistance were found in any of our patients who had a median treatment period of 96.6 weeks. This value is not far from the rates indicated in the literature.

All patients in our study well-tolerated ENT and rates and frequency of ENT-related adverse events were consistent with the literature.[8–10, 14] Lange at al.[15] reported lactic acidosis and related mortality in patients treated with ENT. There were no fatal side effects in our study group, and no patients had to discontinue treatment due to side effects. To the best of our knowledge, there is not sufficient data on the relationship between ENT and renal dysfunction in the literature. The mild renal impairment occurred in our two patients did not require dose reduction or treatment change. However, it should be kept in mind that renal dysfunction may develop with ENT treatment and this should be considered carefully in follow-up.

It is emphasized in the literature that the compliance of the patients with treatment is a sensitive issue in terms of treatment success and prevention of the development of drug resistance.[16] Sustainable results, relatively low side effects, high tolerability and ease of use of a single dose per day were probably active in 100% compliance.

Conclusion

ENT can be preferred as an effective and safe first-line drug in the treatment of patients with NA-naive CHB. Our results should be validated in a larger cohort of patients.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of the University of Health Sciences Okmeydanı Training and Research Hospital (Project number: 2007-0023).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.K., N.Y.; Design – M.K., N.A., N.Y.; Supervision – M.K., N.Y.; Materials – M.K., N.A.; Data collection &/or processing – M.K., N.A., K.K., N.A., N.Y.; Analysis and/or interpretation – M.K., S.K.; Literature search – M.K., N.A.; Writing – M.K., N.Y.; Critical review – M.K., N.A., N.Y.

References

1. Lok AS. Prevention of hepatitis B virus-related hepatocellular carcinoma. Gastroenterology 2004;127:S303–9. [CrossRef]
2. Hepatitis B fact sheet. Geneva: World Health Organization, October 2000. Available at http://www.who.int/mediacentre/factsheets/fs204/en/. Accessed November 11, 2008.
3. Ökten A. Türkiye'de kronik hepatit, siroz ve hepatosellüler karsinoma etiyolojisi. Çakaloğlu Y, Ökten A, editors. Hepatit B, Ulusal Uzlaşma Toplantı Metinleri. İstanbul: İstanbul Medikal Yayıncılık;2003. p.1–7.
4. Keeffe EB, Dieterich DT, Han SH, Jacobson IM, Martin P, Schiff ER, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. Clin Gastroenterol Hepatol 2008;6:1315-41. [CrossRef]
5. Fung J, Lai CL, Seto WK, Yuen MF. Nucleoside/nucleotide analogues in the treatment of chronic hepatitis B. J Antimicrob Chemother 2011;66:2715–25. [CrossRef]
6. Bristol-Myers Squibb Co. Baraclude® (entecavir) prescribing information (online) Available from: http://www.baraclude.com/pi.html
7. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139:137–47. [CrossRef]
8. Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006;354:1001–10. [CrossRef]
9. Gish RG, Lok AS, Chang TT, de Man RA, Gadano A, Sollano J, et al. Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. Gastroenterology 2007;133:1437–44. [CrossRef]
10. Zheng MH, Shi KQ, Dai ZJ, Ye C, Chen YP. A 24-week, parallel-group, open-label, randomized clinical trial comparing the early antiviral efficacy of telbivudine and entecavir in the treatment of hepatitis B e antigen-positive chronic hepatitis B virus infection in adult Chinese patients. Clin Ther 2010;32:649–58.
11. Chang TT, Liaw YF, Wu SS, Schiff E, Han KH, Lai CL, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology 2010;52:886–93. [CrossRef]
12. Sherman M, Yurdaydin C, Simsek H, Silva M, Liaw YF, Rustgi VK, et al. Entecavir therapy for lamivudine-refractory chronic hepatitis B: improved virologic, biochemical, and serology outcomes through 96 weeks. Hepatology 2008;48:99–108. [CrossRef]
13. Tenney DJ, Rose RE, Baldick CJ, Pokornowski KA, Eggers BJ, Fang J, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. Hepatology 2009;49:1503–14. [CrossRef]
14. Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006;354:1011–20.
15. Lange CM, Bojunga J, Hofmann WP, Wunder K, Mihm U, Zeuzem S, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. Hepatology 2009;50:2001–6. [CrossRef]
16. Shouval D, Lai CL, Chang TT, Cheinquer H, Martin P, Carosi G, et al. Relapse of hepatitis B in HBeAg-negative chronic hepatitis B patients who discontinued successful entecavir treatment: the case for continuous antiviral therapy. J Hepatol 2009;50:289–95. [CrossRef]