TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2014) 44: 283-287

doi:10.3906/sag-1211-66

Evaluation of 48-week response of treatment-naive chronic hepatitis B patients to 0.5 mg/day entecavir

Servet KÖLGELİER[1], Nazlım AKTUĞ DEMİR[2], Serap ÖZÇİMEN[3,*], Şua SÜMER[4]

[1]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine , Adıyaman University, Adıyaman, Turkey
[2]Infectious Diseases Clinic, Konya Research and Training Hospital, Konya, Turkey
[3]Infectious Diseases Clinic, Konya Numune Hospital, Konya, Turkey
[4]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Selçuk University, Konya, Turkey

Received: 20.11.2012 • **Accepted:** 22.04.2013 • **Published Online:** 15.01.2014 • **Printed:** 14.02.2014

Aim: The hepatitis B virus (HBV) is an important healthcare problem. Chronic hepatitis B infection may present with a wide range of manifestations from inactive carrier state to cirrhosis and hepatocellular cancer. Therefore, treatment is very important in chronic hepatitis B. In this study, the treatment results of 199 chronic hepatitis B patients taking entecavir 0.5 mg/day for 48 weeks were evaluated.

Materials and methods: This study retrospectively evaluated data of 199 treatment-naive chronic hepatitis B patients who were treated with entecavir.

Results: Of the 199 treatment-naive chronic hepatitis B patients, 141 (70.9%) were males and 58 (29.1%) were females, and mean age of the whole group was 37.5 ± 12.1 years. HBeAg was positive in 91 (45.7%) and antiHBe was positive in 108 (54.3%) patients. Mean HBV DNA value was 666,449,365.5 ± 2,759,013,996.9 IU/mL, mean ALT value was 112.1 ± 95.7 U/L, and mean AST value was 95.3 ± 71.2 U/L. At week 24 of the treatment, HBV DNA levels were below 50 IU/mL in 56% of the HBeAg-positive and 76% of the HBeAg-negative patients. At week 48 of the treatment, HBV DNA levels were below 50 IU/mL in 79% of the HBeAg-positive and 87% of the HBeAg-negative patients. At week 24, ALT had normalized in 72% of the HBeAg-positive and 79% of the HBeAg-negative patients. At week 48, ALT had normalized in 89% of the HBeAg-positive and 88% of the HBeAg-negative patients. AntiHBe seroconversion was seen in 2 of 91 patients (2.2%), but the loss of HBsAg was never observed.

Conclusion: The 48-week entecavir treatment at a dose of 0.5 mg/day was shown to be effective both for HBeAg-positive and negative patients.

Key words: Chronic hepatitis B, entecavir, entecavir efficacy

1. Introduction

Hepatitis B virus (HBV) infections are prevalent in both Turkey and the rest of the world, and chronic hepatitis is the leading chronic viral disease (1,2). Chronic hepatitis B infections may present a wide range of manifestations from the inactive carrier state to cirrhosis and hepatocellular cancer (HCC) (3).

The goals of treatment for CHB are to permanently suppress HBV replication and to relieve hepatic damage. The ultimate target of treatment is the prevention of cirrhosis and hepatocellular cancer (HCC) (4–6). ALT normalization, HBV DNA clearance, HBeAg seroconversion, and improved liver histology may be seen during treatment (7,8).

Entecavir, which is a potent drug recommended in the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) guidelines, was first used for CHB after approval in the US in 2005 and in Turkey in 2007. It is a 2-deoxyguanosine analog, and after triple phosphorylation by the host's cellular kinases it forms entecavir phosphate (ETV-TP). Its half-life is 15 h, similar to lamivudine. ETV-TP inhibits HBV replication in 3 separate steps, which differentiates it from other nucleoside or nucleotide analogs. These steps are inhibition of HBV-DNA polymerase primers, inhibition of negative strand reverse transcription from pregenomic RNA of HBV-DNA, and inhibition of HBV-DNA positive strand synthesis. Triple-step inhibition of HBV highly suppresses HBV-DNA, and in vitro studies showed that entecavir is a stronger antiviral agent than lamivudine and adefovir (4,6,9).

* Correspondence: serapdr@yahoo.com

In our literature review, there were no other studies covering such a high number of patients in this country. In this study, the data of 199 CHB patients treated with 0.5 mg/day of entecavir for 48 weeks were retrospectively evaluated.

2. Materials and methods

This study retrospectively evaluated 199 treatment-naive chronic hepatitis patients who were treated with entecavir. This study was approved by the local ethics committee.

Biopsies were performed as suggested by AASLD criteria. After marking via hepatic ultrasonography, the biopsy was performed with a 16G Hepafix or Tru-cut liver biopsy needle. Samples were sent to the pathology laboratory immersed in a formaldehyde solution. Entecavir 0.5 mg/day was started in patients with chronic hepatitis B in accordance with the Turkish public health system. Patient inclusion criteria were: having no previous treatment for chronic hepatitis B; being over 18 years old; having no compensated or decompensated cirrhosis; having no contraindication for liver biopsy; and those who were not pregnant or breastfeeding.

Before treatment, patients' age, sex, address, phone number, body mass index, occupation, family history, underlying illnesses, symptoms, physical examination findings, laboratory values (thrombocyte, leukocyte, hemoglobin, prothrombin time (PT)), activated partial thromboplastin time (APTT), HBsAg, antiHBs, HBeAg, antiHBe, antiHCV, antiHDV, HBV DNA, ALT, AST, albumin, creatinine, alpha fetoprotein (AFP), radiologic findings (upper abdominal ultrasonography), pathology results (Ishak score, a modified Knodell score, from liver biopsy), and treatment protocols were recorded in patient charts. Clinical complaints, physical examination findings, and laboratory findings (HBV DNA, ALT, AST, and creatinine) during follow-up visits were also recorded on the same chart. Patients were thoroughly evaluated again at the end of week 48, and symptoms, physical examination findings, laboratory values (hemoglobin, PT, APTT, HBsAg, antiHBs, HBeAg, antiHBe, antiHCV, antiHDV, HBV DNA, ALT, AST, albumin, creatinine, phosphate, calcium, ALP, and AFP), and radiologic findings (upper abdominal ultrasonography) were also recorded in the follow-up form.

During the treatment, HBV DNA, ALT, AST, and creatinine values were measured at weeks 4, 12, 24, and 48 and were recorded in patient charts. Data were entered in the SPSS 16.0 software. Categorical data were analyzed by chi-square test, and continuous variables were analyzed by t test and Mann–Whitney U test. To analyze repeated measures, the analysis of variance of repeated measures test was used, and significant results in this test were analyzed by signed rank test. $P < 0.05$ was considered statistically significant.

3. Results

Of 199 treatment-naive chronic hepatitis B patients, 141 (70.9%) were males and 58 (29.1%) were females. The mean age of the general group was 37.5 ± 12.1. Family history was positive in 155 (77.9%) patients (Table 1).

HBeAg was positive in 91 (45.7%) and antiHBe was positive in 108 (54.3%) patients. Mean HBV DNA value was 666,449,365.5 ± 2,759,013,996.9 IU/mL, mean ALT value was 112.1 ± 95.7 U/L, and mean AST value was 95.3 ± 71.2 U/L (Table 2).

During follow-up visits, ALT and HBV DNA values had markedly decreased, and this decrease was statistically significant (P value 0.001 and 0.001, respectively) (Table 3).

In our study, HBV DNA values decreased at each follow-up visit at weeks 0, 4, 12, 24, and 48 after entecavir 0.5 mg/day, and this decrease was statistically significant ($P = 0.01$). The values of HBV DNA at weeks 4, 12, 24, and 48 were significantly lower than values at the treatment's start (P values were 0.01 for all) (Table 3). Additionally, HBV DNA values at the weeks following treatment courses were significantly lower than the values at weeks before treatment courses (P values were 0.02 for all). At week 24, HBV DNA was below 50 IU/mL in 56% of HBeAg-positive and 76% of HBeAg-negative patients. At week 48 of treatment, HBV DNA was below 50 IU/mL in 79% of HBeAg-positive and 87% of HBeAg-negative patients.

ALT values decreased both in HBeAg-positive and negative patients at each follow up visit at weeks 0, 4, 12, 24, and 48 after entecavir 0.5 mg/day, and this decrease was statistically significant ($P = 0.001$). Values of ALT at weeks 4, 12, 24, and 48 were significantly lower than values at the

Table 1. Demographic features of the patients.

	Number	Percent (%)
Sex		
Male	141	70.9
Female	58	29.1
BMI		
0–18.0	5	2.5
18.1–25	138	69.3
25.1–30.0	56	28.1
Family History		
Yes	155	77.8
No	44	22.2

(BMI: Body Mass Index)

Table 2. Patients' laboratory parameters and liver biopsy results (Ishak score, a modified Knodell score).

Laboratory test	Result
ALT (0–40 U/L)	112.1 ± 95.7 U/L
AST (0–40 U/L)	95.3 ± 71.2 U/L
HBV DNA(<20 IU/mL)	666,449,365.5 ± 2,759,013,996.9 IU/mL
HBeAg positivity	45.7%
antiHBe positivity	53.8%
AFP (ng/mL)(0–8 ng/mL)	3.4 ± 2.1 ng/mL
Albumin (3.5–5.5 g/dL)	3.8 ± 0.3 g/dL
Thrombocytes (150,000–400,000/μL)	249,314.6 ± 97,377.5/μL

Table 3. HBV DNA and ALT values at follow-up visits.

	Week 0	Week 4	Week 12	Week 24	Week 48	P value
HBV DNA (IU/mL)	666,449,365.5 ± 2,759,013,996.9	1,561,393 ± 6,897,102	51,094 ± 230,003	4641 ± 25,189	455 ± 1724	0.001
ALT(0–40 U/L)	112 ± 95	62 ± 35	41 ± 16	34 ± 13	28 ± 10	0.001

start of the treatment (P values < 0.01 for all). Moreover, ALT values for the weeks following treatment courses were significantly lower than the values for the weeks before treatment courses (P values were 0.01 for all) (Table 3). By week 24, ALT had normalized in 72% of HBeAg-positive and 79% of HBeAg-negative patients (P = 0.310). By week 48, ALT had normalized in 89% of HBeAg-positive and 88% of HBeAg-negative patients (P = 0.818). At week 48 of treatment, mean ALT value was 28 U/L (range of 13–77).

AntiHBe seroconversion was seen in 2 of 91 patients (2.2%), but loss of HBsAg was never observed.

Patients tolerated the drug well. Nausea was reported by 12 (6%), abdominal pain by 5 (2.5%), diarrhea by 5 (2.5%), and headache by 4 (2%) patients. No other side effects were observed. None of the side effects were significant enough to warrant discontinuation of the treatment.

4. Discussion

Virologic response in chronic hepatitis B treatment is defined as a decrease in HBV DNA to values undetectable by PCR and a loss of HBeAg in patients who were HBeAg positive at the beginning of the treatment (4). Chang et al. (10) measured HBV DNA levels below 300 copy/mL in 236 of 354 patients (67%) at week 48. Zheng et al. (11) followed 66 HBeAg-positive patients treated with entecavir 0.5 mg/day for 24 months. Plasma HBV levels below 500 copy/mL were regarded as undetectable. HBV DNA level decreased to undetectable levels in 23 (34.8%) patients at week 12 of treatment and in 38 patients (57.6%) at week 24 of treatment. Köklü et al. (17) obtained a virologic response in 92.6% of the patients. We found that in HBeAg-positive and negative patients, with 48 weeks of entecavir 0.5 mg/day treatment, HBV DNA levels decreased at each follow-up visit at weeks 0, 4, 12, 24, and 48. This decline was statistically significant. By week 24, HBV DNA levels were below 50 IU/mL in 56% of HBeAg-positive and 76% of HBeAg-negative patients. By week 48, HBV DNA levels were below 50 IU/mL in 79% of HBeAg-positive and 87% of HBeAg-negative patients. Our results were in concordance with the studies by Song et al. (12) and Zheng et al. (11) (Table 4).

AASLD guidelines define a biochemical response as a decrease in plasma ALT to normal levels (4). Gish et al. (16) found that, after 48 weeks of entecavir treatment, ALT normalized in 161 of 243 (66%) patients. Chang et al. (10) measured ALT levels was within normal limits in 242 of 354 (68.3%) patients at week 48. Zheng et al. (11) measured ALT levels within normal limits in 66 of 49 (74.2%) patients by week 24. Köklü et al. found the rate of ALT normalization by week 48 to be 84.7%. We found that ALT levels significantly decreased at each visit on weeks 0, 4, 12, 24, and 48. By week 24 of treatment, ALT

Table 4. Treatment response parameters at week 48.

	HBeAg-positive patients								HBeAg-negative patients				
	Lok and McMahon (4)	Chang et al. (10)	Song et al. (12)	Buti et al. (13)	Chen et al. (14)	Kwon et al. (15)	Gish et al. (16)	Our study	Lok and McMahon (4)	Song et al. (12)	Buti et al. (13)	Chen et al. (14)	Our study
HBV DNA negativity	67%		76.1%	61%	62.5%	55.8%	64.1%		90%	95%	92%	75%	87%
Normalization of ALT	68%			78%				89%	78%		83%		88%
HBeAg loss	22%	22%		26%						23.5%			
Anti HBe seroconversion	21%	21%		22%				2.2%					

had normalized in 72% of HBeAg-positive and 79% of HBeAg-negative patients. By week 48 of treatment, ALT had normalized in 89% of HBeAg-positive and 88% of HBeAg-negative patients. The mean ALT level at week 48 was 26 U/L (range of 13–77) (Table 4).

The HBeAg loss/seroconversion rate was 23.5% in a multicentric study conducted by Köklü et al. (17). However, the lack of patients with HBeAg is noteworthy. We found antiHBe seroconversion in 2 (2.2%) of 91 patients after 48 weeks of treatment with entecavir 0.5 mg/day. The antiHBe seroconversion rates were higher in the literature (4,10,13). However, there have been no reported antiHBe seroconversion rates in Turkey, except the rates published by Köklü et al. (17). The lack of seroconversion rates in our study was related to genotype-D dominance in this country (Table 4). Treatment was continued in 2 patients 1 year after the antiHBe seroconversion.

The ideal result of treatment is HBsAg loss, which is frequently achievable with the currently available anti-HBV agents (6). Lok and McMahon (4) found that a loss of HBsAg was detected in 2% of patients. Chang et al. (10) found HBsAg loss in 7 (2%) of 354 patients taking entecavir at week 48 of treatment. Köklü et al. (17) did not observe HBsAg loss. We did not observe HBsAg loss in any of the patients in the current study.

Entecavir use has been associated with side effects such as mild headache, upper respiratory tract infection, cough, pharyngitis, malaise, upper abdominal pain, and gastrointestinal discomfort (18). Chang et al. (10) reported that common side effects in patients using entecavir were mild to moderate degree headache, upper respiratory tract infection, nasopharyngitis, cough, malaise, upper abdominal pain, and diarrhea. None of these side effects was seen in 306 of 354 (86%) patients. Gish et al. (16) detected fatigue in 6% and headache in 10% of patients. Zheng et al. (11) observed that patients tolerated entecavir well. They detected upper respiratory tract infection in 6 (9.1%), fatigue in 5 (7.6%), diarrhea in 2 (3%), and cough in 1 (1.5%) of 66 patients. All of these side effects were mild to moderate in severity. In our study, we also observed that patients tolerated the drug well. We detected nausea in 12 (6%), abdominal pain in 5 (2.5%), diarrhea in 5 (2.5%), and flatulence in 4 (2%) of 199 patients. We did not observe any side effects other than those mentioned. None of the side effects were serious enough to warrant discontinuation of treatment.

In conclusion, good patient compliance, few side effects, and efficiency in suppressing the infection are the advantages of entecavir. Therefore, entecavir, which is one of the most potent agents for CHB treatment, seems to be effective and safe.

References

1. Ustaçelebi Ş, Ergünay K. Hepatit B virüsünün moleküler virolojisi. In: Tabak F, Balık İ, Tekeli E, editors. Viral Hepatit 2007. İstanbul: Viral Hepatitle Savaşım Derneği; 2007. pp. 96–107.

2. Vyas GN, Yen TSB. Hepatitis B virus: Biology, pathogenesis, epidemiology, clinical description, and diagnosis. In: Specter S, editor. Viral Hepatitis. Diagnosis, Therapy and Prevention. New Jersey, USA: Humana Press; 1999. pp. 35.

3. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. Hepatology 2007; 45: 1056–75.

4. Lok AS, McMahon BJ. AASLD practice guidelines. Chronic Hepatitis B: Update 2009. Hepatology 2009; 50: 661–2.

5. Lok AS, McMahon BJ. AASLD practice guidelines: Chronic hepatitis B. Hepatology 2007; 45: 507–539.

6. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of chronic hepatitis B. J Hepat 2009; 50: 227–242.

7. Saltoğlu N. B tipi kronik hepatitin güncel tedavisi. In: Tabak F, Balık İ, Tekeli E, editors. Viral Hepatit 2005. İstanbul: Viral Hepatitle Savaşım Derneği; 2005. p. 214–32.

8. Nguyen MH, Keeffe EB. Chronic hepatitis B and hepatitis C in Asian Americans. Rev Gastroenterol Dis 2003; 3: 125–34.

9. Yamazhan T. Kronik hepatit B tedavisinde antiviral ile uzun vadeli sonuçlar. In: Tabak F, Balık İ, editors. Viral Hepatit 2009. İstanbul: Viral Hepatitle Savaşım Derneği; 2009. pp. 31–44.

10. Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, Lok AS, Han KH, Goodman Z, Zhu J et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006; 354: 1001–10.

11. 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.

12. Song CJ, Min BY, Kim JW, Kim JY, Kim YM, Shin CM, Lee SH, Hwang JH, Jeong SH, Kim N et al. Pretreatment serum HBsAg-to-HBV DNA ratio predicts a virologic response to entecavir in chronic hepatitis B. Korean J Hepat 2011; 17: 268–273.

13. Buti M, Morillas RM, Prieto M, Diago M, Perz J, Sola R, Bonet L, Palau A, Testillano M, Garcia-Samaniego J et al. Efficacy and safety of entecavir in clinical practice in treatment-naive Caucasian chronic hepatitis B patients. Eur J Gastroenterol Hepat 2012; 24: 535–42.

14. Chen EQ, Zhou TY, Liu L, Liu C, Lei M, Tang H. A comparison of treatment with adefovir and entecavir for chronic hepatitis B in China: The 2-year results of a prospective study. Hepat Mon 2011; 11: 27–31.

15. Kwon JH, Jang JW, Lee S, Lee J, Chung KW, Lee YS, Choi JY. Pretreatment HBeAg level and an early decrease in HBeAg level predict virologic response to entecavir treatment for HBeAg-positive chronic hepatitis B. J Viral Hepat 2012; 19: 41–47.

16. Gish RG, Lok AS, Chang TT, Man RA, Gadano A, Sollano J, Han KH, Chao YC, Lee SD, Harris M et al. Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. Gastroenterology 2007; 133: 1437–44.

17. Köklü S, Tuna Y, Gülşen MT, Demir M, Köksal AŞ, Koçkar MC, Aygün C, Çoban Ş, Özdil K, Ataseven H et al. Long-term efficacy and safety of lamivudine, entecavir and tenofovir for treatment of hepatitis B virus-related cirrhosis. Clin Gastroenterol Hepatol 2013; 11: 88–94.

18. Sims KA, Woodland AM. Entecavir: a new nucleoside analog for the treatment of chronic hepatitis B infection. Pharmacotherapy 2006; 26: 1745–57.