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Efficacy of entecavir treatment among chronic hepatitis B nucleos(t)ide-naïve and -experienced patients

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Background/aim: To evaluate the efficacy of entecavir (ETV) among chronic hepatitis B (CHB) nucleos(t)ide-naïve and -experienced patients in clinical practice.

Materials and methods: In this retrospective study 85 CHB patients who had been receiving ETV and who attended our clinic since 2007 were included. Fifty patients were nucleos(t)ide analogue (NA)-naïve. Factors including sex, positive HBeAg, baseline HBV DNA level, baseline alanine aminotransferase level, and prior lamivudine (LAM) resistance were evaluated in terms of their predictive role in treatment response, which was defined as a serum HBV DNA decrease of <31.4 copies/mL.

Results: Resistance was detected in 18 (51.4%) of 35 lamivudine-experienced patients. Virological response (VR) was achieved in 48 (96.0%) of NA-naïve patients, while 16 (45.7%) of NA-experienced patients achieved VR. LAM-resistant patients had significantly lower response rates ($P < 0.001$). More responders with a low initial viral load achieved VR at the end of the 12-month follow-up period compared to those with a high initial viral load (91.7% vs. 70.0%, $P = 0.004$).

Conclusion: ETV has greater efficacy in NA-naïve patients and in NA-experienced patients without prior LAM resistance. The rate of VR achievement at 12 months was higher in patients who initially had a low viral load with ETV treatment.

Key words: Chronic hepatitis B virus infection, entecavir, efficacy, predictive factors, viral response, lamivudine resistance

1. Introduction

Entecavir (ETV), one of the most promising new nucleos(t)ide analogues (NAs), is a selective guanosine analogue that potently blocks hepatitis B virus (HBV) replication. ETV has a favorable histological, virological, and biochemical profile, with less frequent development of resistance compared to lamivudine (LAM) (1). These properties indicated that ETV could be used to rapidly sustain control of HBV replication (2), which led to major international guidelines recommending it as a first-line therapy for hepatitis B. However, ETV efficacy in NA-experienced patients, as well as its use in cases of partial virological response (VR) frequently encountered in clinical practice, has not yet been clarified (3–5).

The inclusion of selected groups of HBV patients in clinical trials complicates the translation of findings into clinical practice. Furthermore, the increasing number of patients who experience treatment failure to various NA treatment regimens poses a growing problem for the clinician, warranting investigation of the efficacy of ETV in these NA-experienced patient groups (6). The present study was designed to evaluate the efficacy of ETV treatment in clinical practice among NA-naïve and -experienced patients with chronic hepatitis B (CHB) and to identify baseline factors associated with VR to ETV.

2. Materials and methods

2.1. Study population

This retrospective study included 85 CHB patients (mean age: 46.0 ± 13.0 years; 72% male) who received ETV therapy and were followed at the İzmir Bozyaka Teaching and Research Hospital's Infectious Disease and Clinical Microbiology Clinic (İzmir, Turkey) since 2007. The inclusion criteria were HBV DNA of >10,000 copies/mL with moderate fibrosis (≥2 Ishak scoring) and/or necroinflammation or serum alanine aminotransferase (ALT) levels of >2× the upper limit of the normal range (ULN), and completion of a 12-month follow-up period.

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Exclusion criteria included coinfection with hepatitis D virus, hepatitis C virus, or human immunodeficiency virus; immunosuppression and decompensated liver cirrhosis; or failure to complete the 12-month follow-up prior to reaching the study endpoint. Written informed consent was obtained from each patient and the study was approved by the institutional ethics committee.

2.2. Data collection and study parameters

Patients were monitored at 3- or 6-month intervals, during which routine biochemical parameters, including serum hepatitis markers (HBsAg, HBeAg, anti-HBeAb) and virological parameters (HBV DNA), were monitored during the 24-month follow-up. Serum hepatitis markers were tested using commercial enzyme immunoassays. HBV DNA was quantified by a real-time polymerase chain reaction (RT-PCR) assay using the *artus* HBV RG PCR Kit with the QIAGEN Rotor-Gene Q 6000 instrument. The analytic lower detection limit of the assay was 3.8 IU/mL (constant 8.2 to conversion copy 31.4, P = 0.05).

The primary endpoint was VR, defined as a serum HBV DNA decrease of <31.4 copies/mL during the on-treatment follow-up period. Treatment was continued in all of the responders (4,5). Partial VR was when HBV DNA had decreased more than 2 log but was detectable between >31.4 copy/mL and <10,000 copies/mL at the end of the 12-month follow-up period (4,5). The treatment was continued in patients with partial VR. Therapy was discontinued in nonresponders who had not achieved VR or partial VR after the 12-month follow-up period. In nonresponders, a tenofovir/LAM combination regimen was used as a salvage therapy since most had at least 1 genotypic resistance mutation (4,5).

Secondary endpoints were HBsAg loss and seroconversion, HBeAg loss and seroconversion for HBeAg-positive patients, and ALT normalization. Additionally, factors including sex, positive HBeAg, baseline HBV DNA level (copies/mL), baseline ALT level (mg/dL), prior treatment with interferon, prior LAM treatment, prior LAM resistance, and presence of cirrhosis were evaluated for their predictive role in treatment response. The HBV cut-off point was 10^7 copies/mL in accordance with the national drug prescribing policy in 2009 and 2× ULN for ALT based on prior antiviral research (6–8). ALT was measured during the 12-month follow-up in nonresponders, since treatment was stopped in these patients in the second year of the study.

2.3. Study drug

ETV was administered at a dose of 0.5 mg to NA-naïve patients and 1 mg to LAM-experienced patients. In naïve patients with partial VR, the ETV dose was increased to 1 mg based on the manufacturer's recommended dosage for patients with special concerns, such as LAM resistance or decompensated liver disease (9,10).

2.4. Drug resistance

Resistance tests were performed in all of the LAM-experienced patients with an unknown resistance pattern at the beginning of the treatment. These tests were performed by a reference laboratory using a line immune assay and multiplex PCR prior to initiation of treatment, and by pyrosequencing after treatment in 5 of the 6 nonresponding patients.

2.5. Statistical analysis

Statistical analysis was performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Continuous variable comparisons were made via Student's t-test. The log-rank method with adjusted Kaplan–Meier time-curve analyses was used to determine the significance of predictive factors in treatment response. Significant variables were analyzed by a Cox regression model. A dichotomous cut-off point of HBV DNA of $>10^7$ copies/mL was applied, based on accordance with the national drug prescribing policy in 2009 (6). The estimated probability curves for achieving VR were calculated according to a Cox regression model adjusted for the influence of significant variables (Figures 1 and 2) (11). Data are expressed as mean ± standard deviation (SD), minimum–maximum, and percentage as appropriate. All statistical tests were 2-sided and $P < 0.05$ was considered to indicate a significant difference.

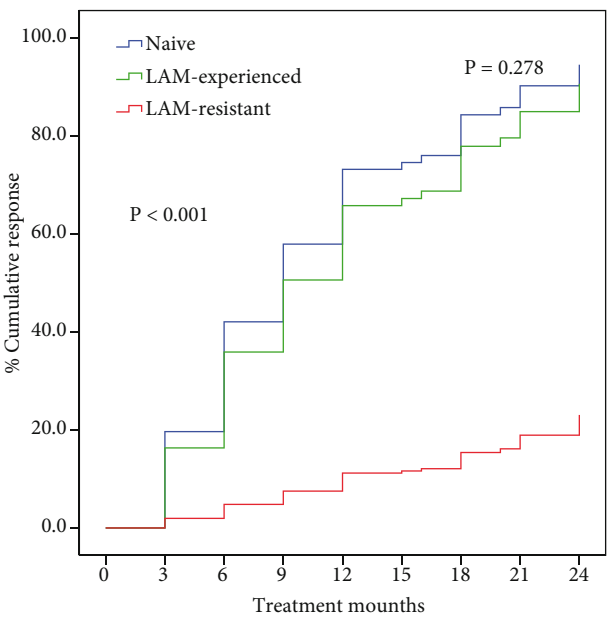

Figure 1. Adjusted estimated curve for the cumulative probability of achieving virological response, defined as HBV DNA of <30 copies/mL for lamivudine-experienced, -resistant, and -naïve patients. These results are based on the Cox regression model for mean values of baseline HBV DNA, ALT level, and HBeAg status.

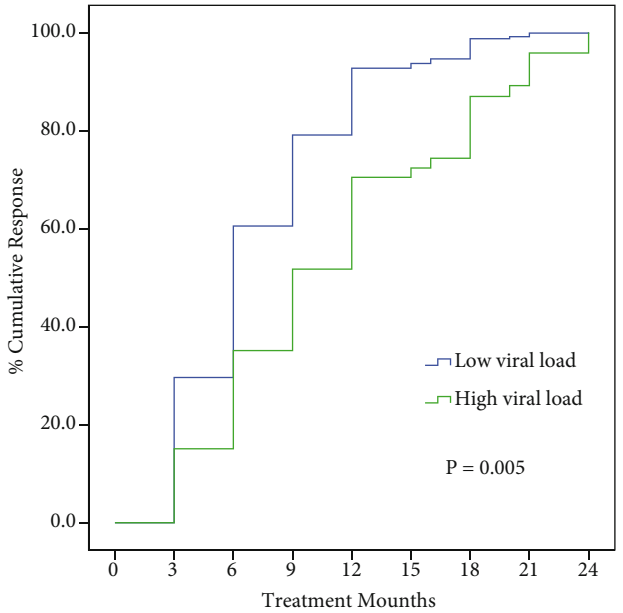

Figure 2. Adjusted estimated curve for the cumulative probability of achieving virological response, defined as HBV DNA of <30 copies/mL, for patients that achieved a treatment response (responders). These results are based on the Cox regression model for the mean ALT level, HBeAg status, and baseline HBV DNA level ($<10^7$ vs. $>10^7$ copies/mL).

3. Results

3.1. Baseline characteristics

The mean age of the 85 included patients was 46.0 ± 13.0 years (72% male), with 50 patients (58.8%) that were NA-naïve (mean age: 47.0 ± 13.0 years, 62% male) and 35 patients (41.2%) that were NA-experienced (mean age: 45.0 ± 11.0 years, 92% male). NA-naïve and NA-experienced patients were of similar age and had equivalent ALT levels (Table 1). Positive HBeAg was detected in 43.5% of the study population. There were significantly more patients with positive HBeAg in the NA-experienced group than in the NA-naïve group (65.7% vs. 28.0%, P = 0.001). Cirrhosis was present in 11.7% of the study population and in significantly more patients in the NA-naïve group than in the NA-experienced group (17.6% vs. 3.0%, P = 0.033) (Table 1).

Prior treatment with pegylated interferon was determined in 47.0% of patients, with significantly more patients in the NA-experienced group than in the NA-naïve group (65.7% vs. 34.0%, P = 0.004). LAM (94.3%), adefovir (34.3%), and tenofovir (5.7%) had been administered previously to NA-experienced patients. Resistance to LAM treatment was found in 51.4% of patients with a prior history of LAM treatment (Table 1).

3.2. Primary endpoint

During a mean follow-up of 40 ± 12 (range: 12–54) months, 48 (96.0%) of the 50 NA-naïve patients achieved VR, defined as HBV DNA of <31.4 copies/mL. Two patients with positive HBeAg who had a high baseline viral load failed to achieve treatment response within 2 years of follow-up. Treatment was switched to tenofovir in these patients and no mutations were detected in genotypic resistance screening performed via pyrosequencing. VR was achieved in 16 (45.7%) of 35 NA-experienced patients during a mean follow-up of 33 ± 14.2 (range: 12–57) months.

3.3. Initial viral load and HBeAg positivity rate in responders during follow-up

An initial high viral load was seen in 40 (62.5%) of 64 responders. The remaining 24 (37.5%) patients initially had a low viral load. At the end of the 12-month follow-up period, VR was achieved in 91.7% (n = 22) of responders with a low initial viral load and in only 70.0% (n = 28) of responders with a high initial viral load (P = 0.004; Table 2).

Of the 64 responders, 17 (26.6%) were positive for HBeAg, while 47 (73.4%) were negative. Evaluation of responders at follow-up visits revealed similar rates of VR achievement in negative and positive responders for HBeAg (80.9% vs. 70.6%, P = 0.38) (Table 2).

3.4. Secondary endpoints

HBsAg loss was not observed in the study population, while HBeAg loss and seroconversion were evident in 3 patients. In 1 of the patients with HBeAg seroconversion during the first year of consolidation therapy, an elevated ALT level and viral load were identified during the second year of the follow-up period, despite the lack of seroreversion. There was an increased trend toward ALT normalization in responders (82.8%) compared to nonresponders (66.6%) at the end of the 12-month treatment period (P = 0.022), while the proportion of responding patients with ALT normalization increased to 93.8% in the second year of treatment.

3.5. Cumulative probability of treatment response

Estimated cumulative probability of treatment response revealed that NA-naïve patients had higher rates of treatment response compared to NA-experienced patients without prior LAM resistance; however, the difference between the 2 groups did not reach statistical significance (P = 0.278). In contrast, LAM-resistant patients had significantly lower response rates compared to NA-naïve and -experienced patients without LAM resistance (P < 0.001) (Figure 1).

In responders, the frequency of achievement of a treatment response at the end of the first year was significantly lower (P = 0.005) in patients with a high viral load ($>10^7$ copies/mL) compared to those with a low viral load ($<10^7$ copies/mL) (Figure 2). However, rates of VR achievement were similar in negative and positive responders for HBeAg (P = 0.34) (Figure 3).

Table 1. Baseline characteristics of patients with respect to prior treatment with nucleos(t)ide analogues (NAs).

	Total (n = 85)	NA-naïve (n = 50)	NA-experienced (n = 35)	P
Age (years)	46.0 (13.0)	47.0 (13.0)	45.0 (11.0)	0.21
Sex (% male)	63 (72.0)	31 (62.0)	32 (91.0)	0.002
ALT (mg/dL)	141.7 (11.3)	157.2 (123.5)	119.4 (88.0)	0.12
HBV DNA (copies/mL)	7×10^8 (2×10^9)	1×10^9 (2×10^{10})	3×10^8 (7×10^9)	0.18
Positive HBeAg	37 (43.5)	14 (28.0)	23 (65.7)	0.001
Cirrhosis	10 (11.7)	9 (17.6)	1 (3.0)	0.033
Prior antiviral treatment				
Pegylated interferon	40 (47.0)	17 (34.0)	23 (65.7)	0.004
Lamivudine total	33 (38.8)	-	33 (94.3)	
Lamivudine experienced	15 (17.6)	-	15 (42.8)	
Lamivudine resistant	18 (21.2)	-	18 (51.4)	
Adefovir	12 (14.1)	-	12 (34.3)	
Tenofovir	2 (2.4)	-	2 (5.7)	

ALT, alanine aminotransferase; HBV, hepatitis B virus.

Table 2. HBV DNA negativity rates of responders according the initial viral load and HBeAg positivity during follow-up visits.

	Responders (n = 64)			Responders (n = 64)		
	High initial viral load of $>10^7$ copies/mL (n = 40)	Low initial viral load $<10^7$ copies/mL (n = 24)	P	HBeAg positive (n = 17)	HBeAg negative (n = 47)	P
Month 3	4 (10.0)	9 (37.5)		1 (5.9)	12 (25.5)	
Month 6	12 (30.0)	16 (66.7)		7 (41.2)	21 (44.7)	
Month 9	20 (50.0)	19 (79.2)		8 (47.1)	31 (66.0)	
Month 12	28 (70.0)	22 (91.7)	0.04	12 (70.6)	38 (80.9)	0.38
Month 15	29 (72.5)	23 (95.8)		12 (70.6)	40 (85.1)	
Month 18	34 (85.0)	24 (100.0)		15 (88.2)	43 (91.5)	
Month 21	38 (95.0)	24 (100.0)		16 (94.1)	46 (97.9)	
Month 24	40 (100.0)	24 (100.0)		17 (100)	47 (100)	

3.6. Resistance surveillance

The mean follow-up times in responders and nonresponders were 34.5 ± 7.8 (range: 12–48) months and 20.6 ± 4.7 (range: 12–24) months, respectively. A total of 11 responders (17.2%) experienced transient virological breakthroughs during follow-up, which returned to negative values with time. Transient virological breakthrough was compatible with suspected nonadherence in 5 (71.4%) of 7 patients. In 1 of these nonadherent patients, progression of fibrosis and development of hepatocellular carcinoma was noted, despite ongoing therapy.

4. Discussion

Evaluation of NA-naïve and -experienced patients with CHB infection revealed an increased efficacy of ETV treatment in NA-naïve patients, in NA-experienced patients without prior LAM resistance, and in responders with a low initial viral load. This suggests that ETV may not be a reasonable therapeutic option in the presence of prior LAM resistance.

Our findings indicated that ETV is a safe and effective therapeutic alternative in CHB patients that achieves a treatment response since it resulted in a response in almost

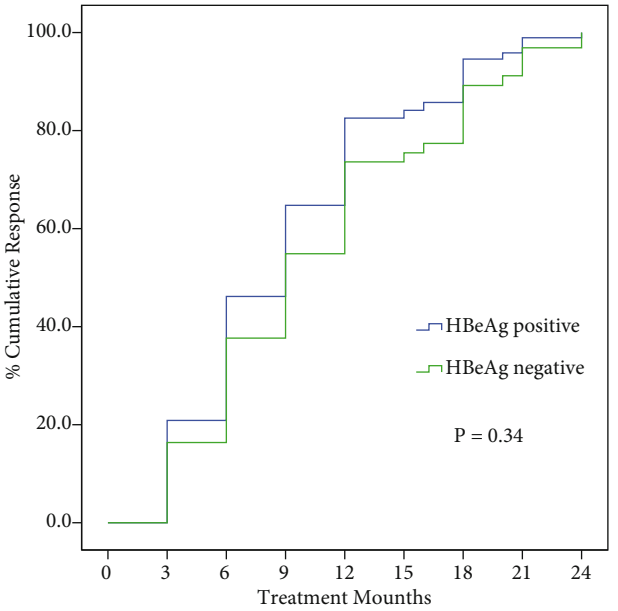

Figure 3. Adjusted estimated curve for the cumulative probability of achieving a virological response, defined as HBV DNA of <30 copies/mL, for HBeAg-negative and -positive patients. The results are based on the Cox regression model for the mean baseline HBV DNA level, mean ALT level, and HBeAg status.

all of the NA-naïve patients after 40 ± 12 months of follow-up. The antiviral effect of ETV in NA-naïve patients in our study confirms that ETV is a highly potent antiviral agent with a good resistance profile within this population (6).

ETV monotherapy is less effective in LAM-refractory patients compared to NA-naïve patients (12–15). Accordingly, our finding of similar ETV treatment response for NA-naïve and NA-experienced patients, coupled with significantly lower response rates in LAM-resistant patients, agreed with previous reports that the antiviral efficacy of ETV was decreased in patients with LAM-resistant mutations at the start of ETV monotherapy. No difference in potency was seen compared to NA-naïve patients in patients previously treated with LAM that did not develop resistance, or in patients with a prior history of LAM-resistance in whom these mutations were not detected at baseline (6,10,13).

Given that almost half of the patients in this study were HBeAg-positive at baseline, it seems notable that patients with HBeAg-positive CHB tended to have higher serum HBV DNA concentrations and a lower likelihood of achieving negative HBV DNA by NA than those with HBeAg-negative CHB, which may be associated with poor VR (15). However, no significant difference was observed between negative or positive responders for HBeAg that achieved VR at the end of the first year.

Despite a higher number of patients with a high initial viral load among overall responders, VR was achieved faster in patients with a low viral load. Hence, given that VR was achieved at the end of a 12-month follow-up period in 91.7% of responders with an initial low viral load and in only 70.0% of patients with a high initial viral load, a high initial viral load was associated with a delay in the treatment response, with achievement of VR at the end of the 24-month follow-up in a third of patients with a high initial viral load. This suggests that long-term follow-up for 24 months, rather than 12 months, allows for VR observation in a significant proportion of patients with a high initial viral load. The continual increase in response rates during the second year of therapy emphasizes that therapy should be continued unchanged if HBV DNA levels continue to decrease at 24 months.

In a previous study of the antiviral effect of ETV in CHB with respect to prior NA exposure, baseline negative HBeAg, high serum ALT, low serum HBV DNA levels, and the absence of LAM-resistant mutations were independent predictors of VR for ETV monotherapy. Thus, ETV was shown to be a potent antiviral agent with a favorable resistance profile in NA-naïve chronic HBV patients (6). Accordingly, ETV has not been recommended as a rescue option for patients with a prior history of LAM-resistance, especially in those positive for HBeAg, although it might still be used in NA-experienced patients without LAM-resistance (6). These initial observations should be confirmed in longer follow-up studies.

Our findings strongly emphasize the fact that a therapeutic response to ETV can be reached after 1 year of treatment in CHB patients, unless there is LAM resistance. It seems notable that exclusion of LAM-resistant patients revealed improved response rates at the end of the second year of therapy, both for HBeAg-positive and -negative groups in our study population.

Similarly, long-term treatment of NA-naïve CHB patients with 0.5 mg/day ETV for 4 years reportedly suppressed HBV DNA to undetectable levels in >90% of patients, regardless of HBeAg status and genotype. Moreover, the drug was safe and rarely induced resistance mutations (16).

Resistant mutants and breakthrough hepatitis were reported to be less frequent during long-term therapy with ETV than with LAM, indicating that ETV is superior for long-term treatment of CHB and cirrhosis patients (16). The lack of detectable mutations after screening for genotype resistance in the majority of our patients with therapeutic failure was associated with either LAM resistance or positive HBeAg, which seems to indicate maintenance of the genetic barrier characteristic of ETV.

The HBeAg seroconversion ratio in our study population seemed to be lower than reported previously. ALT and HBV DNA levels increased in 1 patient during the

second year of follow-up, despite development of HBeAg seroconversion and completion of 1 year of consolidation therapy, which emphasizes the importance of long-term follow up.

Virological breakthrough with mutations related to ETV resistance has been reported in almost one-third of patients with prior LAM resistance, while no virological breakthroughs were documented among patients previously treated with LAM without the development of resistance (6). In our study population, the development of transient HBV DNA elevations mimicking breakthrough in both NA-naïve and -experienced patients that achieved VR was associated with poor adherence to treatment or high analytical sensitivity of HBV DNA rather than actual breakthrough. This supports the crucial role of compliance to treatment, as progression to hepatic fibrosis and hepatocellular carcinoma development were observed in a patient with poor drug compliance with treatment.

In conclusion, retrospective evaluation of both NA-naïve and -experienced patients with CHB revealed that ETV is an effective therapeutic alternative in these patients since treatment response was achieved in almost all of the NA-naïve patients after a mean follow-up of 40 ± 12 months. For the NA-experienced patients, ETV treatment might be an option in the absence of LAM-resistance mutations, but not in those with LAM-resistance mutations.

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