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Evaluation of alanine aminotransferase responses in chronic hepatitis B patients using entecavir or tenofovir disoproxil fumarate

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Ethics Committee Approval
The study was approved by the Izmir Bozyaka Training and Research Hospital Clinical Research Ethics Committee (December 07, 2022 and 2022/170).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: An estimated 300 million individuals worldwide live with hepatitis B virus (HBV) infection. Alanine aminotransferase (ALT) levels, which indicate liver damage when elevated, are among the crucial laboratory parameters frequently monitored in the follow-up of chronic hepatitis B patients. The primary objectives of antiviral treatment are to reduce liver inflammation and prevent the development of hepatocellular carcinoma or cirrhosis by inhibiting HBV replication. This study evaluated ALT responses and identified factors influencing patient responses following initiating entecavir (ETV) or tenofovir disoproxil fumarate (TDF) treatment.

Methods: This retrospective cohort study collected data from treatment-naive and treatment-experienced patients with elevated ALT levels who received either ETV (0.5 or 1 mg per day) or TDF (245 mg per day) treatment between 2008 and 2018. Pregnant women and patients under 18 were excluded from the study. Elevated ALT levels were defined as greater than 35 IU/L for men and 25 IU/L for women. All patients underwent examinations for ALT, HBV DNA levels, HBeAg, and antiHBe at baseline and every 3–6 months. ALT levels of the patients were monitored for 60 months, and the presence of fatty liver was also documented.

Results: Our study comprised 192 patients with a mean age of 53.7 (13.42) years. The majority of patients, 130 (67.7%), were male. Of these, 97 (50.5%) started ETV treatment, while 95 (49.5%) began TDF treatment. The median baseline ALT levels of the patients were 68 (44–133.5) IU/L, and the median ALT levels at the 60th month were 24 (18–32) IU/L. The median initial HBV DNA level was 114,282 (267.5–5,029,875) IU/mL, and the median HBV DNA levels from the 6th month onwards were 0 (0–0). ALT normalization was observed in 44.8% of men and 28.1% of women at 3 months, which was statistically significant (P=0.034). Normalization rates by gender remained consistent in all other months. No significant differences were noted in this regard. ALT normalization rates were 58.5% at the 6th month and 74.7% at the 24th month in the ETV group, significantly higher than in the TDF group (P=0.01, P=0.02, respectively). In patients with fatty liver, ALT normalization rates were significantly lower at 6, 12, 24, and 48 months than those without fatty liver (P=0.01, P=0.01, P=0.009, P=0.002, respectively).

Conclusion: Although ALT responses to ETV treatment were more pronounced in specific months, both drugs demonstrated overall efficacy. ALT levels in patients with fatty liver remained elevated despite antiviral treatment. Therefore, patients with chronic hepatitis B and fatty liver may require additional support beyond antiviral therapy, including metabolic, nutritional, and lifestyle recommendations.

Keywords: hepatitis B, fatty liver, alanine transaminase, tenofovir, entecavir

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Introduction

Currently, it is estimated that approximately 300 million individuals are affected by the hepatitis B virus (HBV) worldwide. In Turkey, the seroprevalence of hepatitis B is approximately 4% [1]. HBV is a DNA virus belonging to the *Hepadnaviridae* family and often presents asymptomatically in infected individuals. The most concerning outcomes associated with this virus are the development of cirrhosis and hepatocellular carcinoma [2]. HBV can be transmitted through various means, including blood contact, sexual transmission, mother-to-baby transmission, and horizontal transmission within families.

Tenofovir and entecavir (ETV) are the most frequently utilized potent antiviral drugs against hepatitis B [3,4]. The primary objectives of antiviral therapy are to diminish liver inflammation and thwart the development of hepatocellular carcinoma or cirrhosis by impeding viral replication. These medications exhibit a high resistance barrier, often necessitating lifelong treatment for patients [5].

Alanine aminotransferase (ALT) stands as one of the paramount laboratory parameters routinely monitored during the follow-up of patients with chronic hepatitis B. Elevated levels of this enzyme can serve as an indicator of liver damage, making regular monitoring an essential tool for healthcare providers in managing this condition and facilitating any required treatment adjustments. The expectation is that using potent antiviral medications, which inhibit viral replication, will suppress liver damage.

The study aimed to evaluate ALT responses and identify factors influencing these responses in patients following the initiation of either entecavir (ETV) or tenofovir disoproxil fumarate (TDF) treatment.

Materials and methods

We collected data from treatment-naive and treatment-experienced patients who exhibited elevated ALT levels and were initiated on either ETV (0.5 or 1 mg per day) or TDF (245 mg per day) treatment between 2008 and 2018. Pregnant women and individuals under 18 were excluded from this study. Treatment-experienced patients had previously received either lamivudine or adefovir dipivoxil. The reasons for patients switching to TDF or ETV included high ALT levels, elevated HBV DNA levels, and/or the presence of side effects. Ethical approval for this study was granted by the local ethics committee on 7/12/2022 under reference number 2022/170 (Ethics Committee of Izmir Bozyaka Training and Research Hospital).

We employed a modified ISHAK scoring system to assess liver biopsies. Following this system, fibrosis stage 3 and beyond signify the progressive impact on the liver [6]. A Histological Activity Index (HAI) score of ≥6 indicated significant hepatic inflammation. Liver biopsy results were included for those individuals for whom data were accessible.

All patients underwent periodic examinations for ALT, HBV DNA levels, HBeAg, and antiHBe at baseline and every 3–6 months. HBV DNA quantification was performed using the *Artus* HBV RG PCR Kit with the QIAGEN Rotor-Gene Q 6000 device (Valencia, CA, USA), which boasts the lowest detection limit of 3.8 IU/mL.

Elevated ALT levels were defined as exceeding 35 IU/L for men and 25 IU/L for women, as per reference [7]. ALT levels of the patients were monitored over 60 months.

Cirrhosis was defined by a nodular liver structure as observed in ultrasonography, signs of portal hypertension such as splenomegaly or varices, and/or a thrombocytopenia count of less than 150,000/mm^3. Additionally, individuals with a fibrosis stage of 4 or higher in liver biopsy results were categorized as having cirrhosis. Patients with fatty liver were also documented.

Diagnosing hepatocellular carcinoma (HCC) was established through dynamic liver magnetic resonance imaging or liver biopsy.

Statistical analysis

Categorical variables were analyzed using descriptive statistics, presented as numbers and percentages. For continuous variables, those conforming to a normal distribution are reported as mean and standard deviation, while those not following a normal distribution are presented as median and interquartile range (IQR). When there were two independent groups, categorical variables were compared using the Pearson chi-square test, while the Cohran Q test was employed for dependent variables with more than two measurements. Statistical analysis was conducted using SPSS 22.0 (IBM Corporation, Armonk, New York, United States), and a two-tailed $P<0.05$ was considered statistically significant.

Results

Our study involved 192 patients with an average age of 53.7 years (standard deviation: 13.42). Most patients, specifically 130 individuals (67.7%), were male. The rate of individuals who initiated either ETV or TDF treatment was 50.5% (n=97) and 49.5% (n=95), respectively. The proportion of patients with prior treatment experience was 46.4% (n=89). In non-naive patients, the mean duration of treatment before changing therapy was 5.26 years (standard deviation: 3.25).

Table 1: Demographic and clinical characteristics of the patients.

Characteristic	n (%)
Age (mean [SD])	53.7 (13.42
Gender	
Female	62 (32.3)
Male	130 (67.7)
Treatment experience	
Yes	89 (46.4)
No	103 (53.6)
Antiviral treatment	
ETV	97 (50.5)
TDF	95 (49.5)
Fatty liver	
0	134 (70.2)
1	42 (22)
2	11 (5.8)
3	4 (2.1)
Cirrhosis	
Yes	14 (7.3)
No	178 (92.7)
HCC	
Yes	5 (2.6)
No	187 (97.4)
E serology before treatment	
HBeAg	54 (29)
Anti hBe	126 (67.7)
HBeag+Anti hBe	6 (3.2)
F score median (IQR)	2 (1-3)
HAI median (IQR)	8 (6-9)

n: number, SD: standard deviation, IQR: interquartile range

Cirrhosis was observed in 14 cases (7.3%), while five cases (2.6%) had HCC. Table 1 presents the demographic and clinical characteristics of the patients.

The patients had a median baseline ALT level of 68 IU/L (range: 44–133.5 IU/L), and at the 60th month, the median ALT level was 24 IU/L (range: 18–32 IU/L). The median initial HBV DNA level was 114,282 IU/mL (range: 267.5–5,029,875 IU/mL), and from the 6th month onwards, the median HBV DNA levels were consistently at 0 (range: 0–0 IU/mL). The 5-year ALT and 2-year HBV DNA follow-up results of the patients are given in Table 2.

Although all patients initially had elevated ALT levels, the ALT normalization rate at 12 months reached 67.7%, and at 60 months, it increased to 73.2%. A statistically significant increase in ALT normalization rates was observed over the 5-year follow-up period (P<0.001) (Table 3).

Table 2: Five-year ALT and 2-year HBV DNA follow-up results.

Months	ALT levels-IU/L Median (IQR)	HBV-DNA levels-IU/mL Median (IQR)
0(n=192)	68 (44-133.5)	114282 (267.5-5029875)
3(n=173)	35 (26-53)	29 (0-514.5)
6(n=188)	29 (23-41.7)	0 (0-46)
12(n=186)	27 (21-36.2)	0 (0-0)
24(n=185)	24 (20-36)	0 (0-0)
48(n=175)	25 (19-34)	-
60(n=157)	24 (18-32)	-

IQR: interquartile range, ALT: alanine aminotransferase

Table 3: ALT normalization rates by months.

	ALT normalization		
Months	**Yes n (%)**	**No n (%)**	***P*-value**
0	0 (0)	192 (100)	<0.001
3	68 (39.3)	105 (60.7)	
6	93 (49.5)	95 (50.5)	
12	126 (67.7)	60 (32.3)	
24	123 (66.5)	62 (33.5)	
48	118 (67.4)	57 (32.6)	
60	115 (73.2)	42 (26.8)	

ALT: alanine aminotransferase

ALT normalization was observed in 44.8% of men and 28.1% of women at 3 months, and this difference was statistically significant (P=0.034). Normalization rates based on gender remained consistent throughout the remaining months, with no notable differences observed. In the ETV group, ALT normalization rates were 58.5% at the 6th month and 74.7% at the 24th month, significantly higher than those in the TDF group (P=0.01, P=0.02, respectively).

For patients with fatty liver, ALT normalization rates were consistently lower at 6, 12, 24, and 48 months than those without fatty liver (P=0.01, P=0.01, P=0.009, P=0.002, respectively). A comprehensive comparison of ALT normalization rates during the follow-up period based on the demographic and clinical characteristics of the patients is provided in Table 4.

No significant differences were observed between the groups with and without ALT normalization at the 3rd, 6th, 12th, 24th, 48th, and 60th months regarding age, F score, and HAI scores. ALT normalization status based on age, F score, and HAI scores is presented in Table 5.

Table 4: Comparison of ALT normalization rates during the follow-up regarding patients' demographic and clinical characteristics.

	ALT normalization											
Variables	**3rd month**		**6th month**		**12th month**		**24th month**		**48th month**		**60th month**	
	Yes n (%)	**No n (%)**	**Yes n (%)**	**No n (%)**	**Yes n (%)**	**No n (%)**	**Yes n (%)**	**No n (%)**	**Yes n (%)**	**No n (%)**	**Yes n (%)**	**No n (%)**
Gender												
Female	16(28.1)	41(71.9)	26(41.9)	36(58.1)	37 (61.7)	23(38.3)	39 (65)	21(35)	37 (64.9)	20(35.1)	37 (72.5)	14(27.5)
Male	52(44.8)	64(55.2)	67(53.2)	59(46.8)	89 (70.6)	59 (29.4)	84 (67.2)	41(32.8)	81 (68.6)	37 (31.4)	78 (73.6)	28 (26.4)
P-value	0.034		0.14		0.22		0.76		0.62		0.89	
Treatment experience												
No	34 (36.2)	60(63.8)	54 (54)	46(46)	72 (72.7)	27(27.3)	67 (68.4)	31(31.6)	62 (68.1)	29(31.9)	62 (78.5)	17(21.5)
Yes	34 (43)	45 (57)	39(44.3)	49(55.7)	54 (62.1)	33 (37.9)	56 (64.4)	31(35.6)	56 (66.7)	28 (33.3)	53 (67.9)	25 (32.1)
P-value	0.35		0.18		0.12		0.56		0.83		0.14	
Antiviral treatment												
ETV	33 (37.9)	54 (62.1)	55(58.5)	39(41.5)	67 (72.8)	25 (27.2)	68 (74.7)	23(25.3)	59 (68.6)	27(31.4)	58 (75.3)	19(24.7)
TDF	35 (40.7)	51 (59.3)	38(40.4)	56(59.6)	59 (62.8)	35 (37.2)	55 (58.5)	39(41.5)	59 (66.3)	30 (33.7)	57 (71.3)	23 (28.7)
P-value	0.71		0.001		0.14		0.02		0.74		0.56	
Fatty liver												
No	52 (41.9)	72 (58.1)	73(55.3)	59(44.7)	96 (73.8)	34 (26.2)	92 (72.4)	35(27.6)	91 (74.6)	31 (25.4)	83 (76.9)	25 (23.1)
Yes	16 (33.3)	32 (66.7)	20(36.4)	35(63.6)	30 (54.5)	25(45.5)	30 (52.6)	27(47.4)	26 (50)	26 (50)	31 (64.6)	17 (35.4)
P-value	0.30		0.01		0.01		0.009		0.002		0.11	

Table 5: ALT normalization status according to age, F, and HAI scores.

	ALT normalization											
Variables	**3rd month**		**6th month**		**12th month**		**24th month**		**48th month**		**60th month**	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Age Mean(SD)	56.1 (14.2)	52.5 (12.6)	53.7 (14)	53.6 (13.7)	54 (13.6)	53.6 (13)	54 (8)	53.1 (13)	55.4 (12.8)	52.8 (13.8)	55.7 (12.9)	51.4 (12.9)
P-value	0.09		0.95		0.95		0.42		0.20		0.068	
F scores Median(IQR)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-2.25)	2 (1-3)	2 (1-3)	2(1-3)	2 (1-3)	2 (1-3)	2 (1-3)
P-value	0.71		0.44		0.66		0.48		0.87		0.47	
HAI scores Median (IQR)	8 (6-10)	7 (6-9)	8(6-9.25)	7 (6-9)	8 (6-9)	8 (6-9)	8 (6-9)	8(6-10)	8 (6-9)	7.5 (6-9)	8 (6-9)	8 (6-9)
P-value	0.06		0.91		0.81		0.6		0.59		0.47	

IQR: interquartile range, ALT: alanine aminotransferase, SD: standard deviation

Discussion

It is essential to emphasize that despite reducing the overall prevalence of hepatitis B, the number of affected patients, morbidity, and mortality rates remain significant. Antiviral treatments can lead to successful virological, serological, and biochemical responses. This can be crucial in preventing adverse outcomes like cirrhosis and hepatocellular carcinoma (HCC), offering substantial relief to individuals afflicted by hepatitis B [8].

Expectations are that chronic hepatitis B patients who consistently adhere to their antiviral treatment regimen will exhibit treatment responses over several years. It is worth highlighting that achieving virological, serological, and biochemical responses is pivotal for effectively managing hepatitis B. Our study assessed ALT responses over 5 years, revealing that ETV demonstrated superior efficacy at the 6th and 24th months, while both drugs exhibited ALT responses during the remaining months. Furthermore, both ETV and TDF treatments displayed substantial reductions in HBV DNA levels starting from the 6th month. A study conducted by Batirel et al. [9] found no significant difference in ALT responses between patients receiving ETV and those receiving TDF. Virological responses were also comparable across all groups. Another study assessing histological responses in patients receiving TDF or ETV revealed that both groups exhibited similar ALT and virological responses [10]. Based on the findings from these studies, it is evident that both drugs have demonstrated success in terms of virological and biochemical responses.

Hepatocellular carcinoma (HCC) is indeed a worrisome consequence of hepatitis B. Several studies propose that the early normalization of ALT levels following treatment could potentially reduce the risk of HCC in individuals with hepatitis B [11]. The results of our study underscore a notable contrast in the utilization of ETV between patients who achieved ALT normalization and those who did not. It is important to note that only five patients in our study developed HCC; some had pre-existing HCC at the outset of their ETV/TDF treatments. Consequently, no statistical analysis was conducted in this regard.

Hepatitis B and fatty liver can coexist, potentially leading to more severe liver damage. Fatty liver often results from metabolic disorders, nutritional issues, and a sedentary lifestyle. Elevated ALT levels can commonly occur due to hepatitis B or fatty liver [12]. Our research revealed that patients with fatty liver experienced persistent high ALT levels despite consistent antiviral treatment. Another study, encompassing patients with metabolic dysfunction-associated fatty liver and hepatitis B, demonstrated that the coexistence of chronic hepatitis B and hepatic steatosis led to elevated ALT enzyme levels and adverse outcomes [13]. Monitoring liver enzymes in chronic hepatitis B patients and conducting annual abdominal ultrasounds to detect fatty liver are crucial practices. Furthermore, investigating metabolic conditions can assist in identifying necessary dietary adjustments and lifestyle changes to enhance liver health.

Limitations

It is important to recognize that our study has certain limitations warrant consideration. Firstly, the study was conducted at a single center, which may restrict the generalizability of our findings to other populations or settings. Additionally, the sample size of patients was relatively small, potentially affecting the statistical robustness of our results. Furthermore, it is essential to note that the study group was not homogeneous, comprising patients with varying treatment experiences and some individuals with pre-existing HCC and/or cirrhosis at ETV/TDF therapy initiation.

Conclusion

Although we observed more pronounced ALT responses to ETV treatment during specific months, both drugs succeeded. Nevertheless, it is worth highlighting that patients with fatty liver continued to exhibit elevated ALT levels despite receiving antiviral treatment. This suggests that individuals with chronic hepatitis B and fatty liver may necessitate additional interventions beyond antiviral therapy, such as addressing metabolic, nutritional, and lifestyle factors. Tailoring support to meet each patient's unique needs and providing comprehensive care for their overall health and well-being is imperative. Furthermore, there is potential for conducting prospective cohort studies involving homogeneous patient groups to investigate how fatty liver impacts the biochemical response to antiviral treatments in hepatitis B patients.

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