

Are nucleot(s)ide analogues a negative factor for HBsAg seroconversion in acute hepatitis B?

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Abstract

Background and study aim: There are several studies comparing patients treated with lamivudine and those not given antiviral therapy in acute hepatitis B. Some of these studies showed that antiviral treatment significantly contributed to survival, whereas one other study suggested that antiviral treatment had no effect. The aim of this study was to investigate the efficacy of tenofovir disoproxil fumarate (TDF) therapy and its effect on HBsAg seroconversion in patients with acute viral hepatitis B.

Patients and methods: The files of 126 patients who were under follow-up for acute HBV infection in the Department of Gastroenterology were analyzed retrospectively. Demographic data, molecular, ELISA, and biochemistry tests at the time of diagnosis and in the follow-up, period were evaluated using the hospital automation system.

Results: The rate of chronicity of HBV was found to be higher in the TDF group than in the group without antiviral treatment. The rate of protective anti-HBs acquisition was found to be lower in the TDF group ($p < 0.05$).

Conclusion: Antiviral treatment with TDF in acute HBV infection may increase the rate of chronicity. It may reduce the development of natural immunity. Further studies are warranted. (*Acta gastroenterol. belg.*, 2024, 87, 367-371).

Keywords: acute hepatitis B, seroconversion, reactivation.

Introduction

Hepatitis B virus (HBV) is a member of the hepadnavirus group and has partial double-stranded DNA. The most common type of serum hepatitis transmitted parenterally is HBV (1). There are approximately 257 million people infected with HBV worldwide. The worldwide prevalence was estimated to be 3.5% in 2015 (2). Turkey is a medium endemic country for Hepatitis B (3).

Acute hepatitis B is usually asymptomatic but has a broad clinical spectrum that can lead to acute liver injury and acute liver failure (1). In adult patients, 1/3 may be symptomatic (4). In symptomatic patients, conservative treatment is usually recommended. Antiviral therapy is generally recommended in patients with a total bilirubin (TB) level > 3 mg/dL for more than 28 days with prolonged jaundice, a coagulopathy with an international normalized ratio (INR) > 1.5 , or one of the signs of severe hepatitis such as ascites or encephalopathy (5).

There are several studies comparing lamivudine-treated and treatment-naïve patient groups. Some of these studies showed that antiviral treatment significantly contributed to survival, whereas one other study suggested that antiviral treatment had no effect (6-8).

This study aimed to evaluate the efficacy of TDF treatment on immunity and the development of chronic infection by comparing the groups of patients diagnosed with acute hepatitis B with and without antiviral treatment.

Material and methods

Study population

The files of 126 patients who were followed up for acute HBV infection between 01.01.2010 and 31.10.2021 in the Gastroenterology Department were analyzed. Three patients who were in the window period were excluded. The data were analyzed retrospectively with the approval of the Non-Interventional Clinical Research Ethics Committee under the Declaration of Helsinki, patient rights regulations and ethical rules.

Evaluation of acute hepatitis B

The diagnosis of acute HBV infection is primarily based on the detection of blood HBsAg and anti-HBc IgM (9). The past health records of the patients were examined and it was determined that these patients had never encountered hepatitis B virus serologically in the 2 years before they were diagnosed with acute hepatitis. Radiological imaging performed with computed tomography or ultrasound showed no findings in favor of chronic liver disease or portal hypertension. The fact that no pathology is detected radiologically supports our diagnosis. Patients in whom reactivation was excluded and who met these diagnostic criteria were considered to have acute HBV infection. HBsAg positivity for more than 6 months is considered a chronic infection (10). Patients who met this criterion were considered to be chronically ill. Patients' age, gender, HBV-DNA, AST, ALT, ALP, gamma-glutamyl transferase (GGT), TB, INR, direct bilirubin (DB), Anti-HBs, HBsAg, HBeAg, Anti-HBe, Total Anti-HBc, Anti-HBc, Anti-HBc IgM,

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Alpha-fetoprotein (AFP) levels at the time of diagnosis and in regular follow-ups after diagnosis were evaluated using the hospital automation system. These parameters were evaluated at the time of diagnosis in patients, 6 months and 1 year after diagnosis in patients without seroconversion, and at the time of seroconversion in patients with HBsAg seroconversion. None of these patients had a history of immunosuppressive therapy or immunodeficiency, infection with hepatitis C, hepatitis D, hepatitis A, or human immunodeficiency virus. In 17 patients who underwent transplantation due to fulminant hepatitis and 2 patients with exitus lethalis, only demographic data were used. Patients were assigned into two groups with and without antiviral treatments. Patients for whom the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), and Asian-Pacific hepatitis B management guidelines recommend antiviral therapy were given antiviral therapy, while other patients did not. (Although there was an indication for antiviral treatment, 4 patients who applied from an external center were followed up by the center to which they were referred without antiviral treatment. These patients were followed up without antiviral therapy as they tended to improve laboratory ally and clinically).

Statistical analysis

The analyses were evaluated in the SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) 22 package program. Descriptive data were presented as number (n) and percentage values for categorical data and mean $\pm$ standard deviation (mean $\pm$ SD) and median (minimum-maximum) values for continuous data. Chi-square analysis (Pearson Chi-square) was used to compare intergroup categorical variables. The suitability of continuous variables for normal distribution was evaluated by Kolmogorov-Smirnov/Shapiro-Wilk test. Mann Whitney U-test was used for the comparison of paired groups since all variables did not conform to normal distribution. The statistical significance level was accepted as $p < 0.05$ in the analyses.

Results

A fulminant course was observed in 13.8% of all patients followed in the acute hepatitis B clinic. Therefore, liver transplantation was performed in these patients and 2% of them developed exitus letalis. TDF was used as an antiviral treatment agent in the patients included in the study. The mean age of the patients included in the study was 38.6 ± 12.0 years in the group given TDF and 39.9 ± 14.7 years in the group not given antiviral treatment. The proportion of males was 66% in the group given TDF and 63.2% in the group not given antiviral treatment. Statistically, the two groups were similar in terms of age and gender ($p > 0.05$) (Table 1).

The biochemical data of the patients in both groups were examined and compared statistically. (Table 1). The

ELISA values of the patients at the time of diagnosis and the statistical comparison results of these values are given in Table 1. Both groups had an HBV DNA positivity rate of 100%. HBeAg positivity rate was 60.5% in the treated group and 61.7% in the group without antiviral treatment (Table 1).

The level of chronicity of the TDF group was 30.4%, while this level was 10.6% in the group without antiviral treatment. The rate of protective anti-HBs acquisition was 56.5% in the TDF group and 78.8% in the group without antiviral treatment. Statistical analysis of the level of chronicisation and protective anti-HBs acquisition showed a significant difference between both groups ($p < 0.05$) (Table 2).

The median time to anti-HBs seroconversion was 142.5 (mean 163.4 ± 121.6) in the TDF group and 169 (mean 168.8 ± 88.8) in the group without antiviral treatment. The time to seroconversion was not significantly different between the two groups ($p > 0.05$). At 1 year, the median value of anti-HBs was 21.2 (mean 194.9 ± 331.4) in the treated group and 56.4 (mean 247.0 ± 342.9) in the group without antiviral treatment. There was no significant difference between both groups in terms of anti-HBs value ($p > 0.05$) (Table 2).

At the end of 1 year, HBV DNA positivity was detected in 3 patients (6.4%) in the TDF group and in 2 patients (3.6%) in the group without antiviral treatment. HBV DNA negativity rate was 93.6% in the TDF group and 96.4% in the group without antiviral treatment. In these cases, HBsAg was positive at the end of 1 year.

Discussion

The diagnosis of acute HBV infection is primarily based on the detection of blood HBsAg and anti-HBc IgM. The replication indicator HBV DNA and HBeAg can be detected (9). In the Clinical Practice Guideline on the Management of Hepatitis B Virus Infection published by the EASL in 2017, specific antiviral treatment is not recommended since 95% of acute hepatitis B infection will resolve spontaneously. Antiviral treatment with nucleot(s)ide analogs has been recommended in patients with coagulopathy, prolonged clinical symptoms, and signs of acute liver failure (11). Similar recommendations have also been made in the guidelines published by the American Association for the Study of Liver Diseases in 2018 (10).

In a review of epidemiological studies conducted in Turkey, the prevalence of hepatitis B was found to be lower under the age of 15 and over the age of 65 and higher between the ages of 15 and 65 (12). The mean age of both groups analyzed in our study was found to be consistent with the literature. In our country, the prevalence of HBV is higher in men than in women (13). In our study, the proportion of men was over 60% in both patient groups, in accordance with the literature.

Perillo et al. proved in 1986 that anti-HBc IgM may be helpful in the diagnosis of acute hepatitis B. They

Table 1. — Demographic data and laboratory values at the time of diagnosis of patients who were not given antiviral treatment and patients who were given TDF

Parameter	Normal Range	Without antiviral treatment	Received TDF	P Value
Median age (range)		39.0 (20-82)	34.0 (21-69)	0.89
Gender: Male/Female		36/21	31/16	0.76
Laboratory values at the time of diagnosis (Mean ±Standard Deviation)				
AST U/L	8-33	1371.06 ± 581.2	1501.2 ± 802.5	0.781
ALT U/L	10-40	2022.7 ± 790.8	2135.5 ± 713.3	0.323
ALP IU/ml	40-130	171.7 ± 64.5	183.1 ± 62.6	0.713
GGT U/L	5-65	253.0 ± 267.1	142.1 ± 80.9	0.905
Total Bilirubin mg/dL				
0.1-1.2	11.5 ± 9.0	15.1 ± 6.8	0.364	
Direct Bilirubin mg/dL				
0-0.4	9.2 ± 7.5	10.7 ± 5.4	0.650	
INR	0.8-1.1	1.2 ± 0.2	1.6 ± 0.6	0.008
Anti-HBc Total				
COI 0-1	7.2 ± 2.3	6.9 ± 5.8	0.131	
Anti-HBc IgM				
COI 0-1	23.5 ± 12.1	22.6 ± 15.5	0.864	
HBsAg				
COI 0-1	2133.3 ± 1293.4	1719.5 ± 1120.7	0.203	
Anti-HBs				
mIU / ml	0-10	1.0 ± 2.2	2.3 ± 6.5	0.891

TDF: Tenofovir Disoproxil AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline phosphatase, GGT: Gamaglutamyl transferase, INR: International normalised ratio, AFP: Alphafeto protein, Anti-HBc IgM: Immunoglobulin M type antibody to hepatitis B core antigen, Anti-HBc Total: Total antibody to hepatitis B core antigen, Anti-HBs: Hepatitis B surface antibody, HBsAg: Hepatitis B surface antigen.

Table 2. — Rate of chronicity, Time to develop seroconversion and Anti-HBs level in patients with seroconversion

Parameter	Without antiviral treatment	Received TDF	P Value
Chronicity: +/-	5 (10.6%) / 42 (89.4%)	14 (30.4%) / 32 (69.6%)	0.018
Protective-level anti-HBs development: +/-	37 (78.8%) / 10 (21.2%)	26 (56.5%) / 20 (43.4%)	0.047
HBs-Ag negative, Anti-HBs negative, HBV-DNA negative:	5(10.6%)	4(8.6%)	1
Time to Anti-HBs seroconversion at one year (days): Mean ± SD	168.9 ± 88.9	163.4 ± 121.6	0.26
Level of Anti-HBs at one year: Mean ± SD	247.0 ± 342.9	194.9 ± 331.4	0.11

TDF: Tenofovir Disoproxil, Anti-HBs: Hepatitis B surface antigen

suggested to using it as a marker for acute infection in patients positive for HBsAg (14). In both groups, all patients had high titer HBsAg and anti-HBc IgM positivity at the time of diagnosis in line with the literature. Anti-HBs provides protective immunity against HBV (15). Both groups had low titers of mean anti-HBs, respectively, and were found to be susceptible to the virus. All patients in both groups were found to have HBV DNA, and active replication was observed.

In the AASLD guideline published in 2018, treatment is recommended when total bilirubin >3 mg/dL or direct bilirubin >1.5 mg/dL (10). EASL has not established any limit value for bilirubin (11). The Asian-Pacific hepatitis B management guideline has set the indication limit for bilirubin treatment at >10 mg/dL (16). According to all 3 guidelines, coagulopathy is an indication for treatment (10,11,16). In our study, patients

were initiated treatment according to the indications in the light of the guidelines.

Tenofovir disoproxil fumarate is a nucleot(s)ide analog that is effective against retroviruses, including hepadnaviruses (17). No mutation of tenofovir resistance has been identified among patients receiving TDF for the treatment of chronic HBV infection (18). In our study, we aimed to observe the seroconversional and biochemical effects of this potent antiviral agent on acute hepatitis B.

In a study by Ito et al. in Japan, which evaluated patients who received antiviral treatment with entecavir or lamivudine and those who did not receive antiviral treatment, they concluded that in general, the duration of HBsAg positivity was significantly higher in the group receiving antiviral treatment. However, they demonstrated that in acute hepatitis B patients infected, HBsAg clearance occurs in a shorter time when antiviral

treatment is started in less than 8 weeks and antiviral treatment reduces the possibility of chronicity (19). The EASL guideline published in 2017 reports that antiviral treatment has no adverse effect on chronicity, referring to these and similar studies (11). In our study, HBsAg positivity was detected after 1 year in 14 (30.4%) patients who received TDF and in 5 (10.6%) patients who did not receive antiviral treatment. Comparison of both groups showed that treatment with TDF significantly increased chronicity ($p=0.018$).

Following infection with HBV, detection of anti-HBs is associated with viral clearance. It is an indicator of immunity against HBV (20). In the study conducted by Kumar et al., the rates of protective anti-HBs development were found to be lower in the group treated with lamivudine compared to the placebo group, but no statistically significant difference was found (7). In the study by Streinu-Cercel et al, a statistically significant higher rate of anti-HBs seroconversion occurred within 6 months in the group treated with entecavir compared to the group not receiving antiviral treatment. In the group treated with lamivudine, seroconversion was lower than in the untreated group (21). In a study by Jochum et al. evaluating patients receiving treatment with different antiviral agents, 20% of patients failed to develop anti-HBs at a protective level (22). In our study, 57.8% of the group treated with TDF developed protective anti-HBs and seroconversion at 1 year, whereas this rate was 77.1% in the group not receiving antiviral treatment indicating that antiviral treatment statistically significantly reduced seroconversion ($p=0.047$). Although Streinu-Cercel et al. showed that more seroconversions occurred in the group treated with entecavir, which is a NUC, the number of patients receiving entecavir in this study was limited to 21 (21). In contrast to this study, TDF in the NUC group decreased the seroconversion rate in our study. In patients achieving anti-HBs positivity, seroconversion occurred in an average of 163.4 days in the TDF group and in an average of 168.9 days in the group without antiviral treatment. There is no statistically significant difference in the time to seroconversion ($p=0.26$). The mean anti-HBs levels were 194.9 IU/l and 247.0 IU/l, respectively. Although the mean level in the group that was not given antiviral treatment was found to be higher, there was no statistically significant difference ($p=0.11$). Both groups show a normal level of immunity.

In the study conducted by Streinu-Cercel et al., the seroconversion rates of HBeAg positive patients to anti-HBeAg after 6 months were 76.4% in the lamivudine group, 47.36% in the entecavir group and 74% in the group receiving no antiviral treatment and no significant difference was found (21). In the study conducted by Kumar et al. with patients receiving lamivudine and control group, HBeAg seroconversion was not significantly different (7). In our study, HBeAg seroconversion rate was 76.9% in the group receiving TDF was higher in favour of the group receiving no treatment with a rate of 89.7% but there was no statistically significant difference

($p=0.28$). This result supports both of these studies.

The main limitations of our study are its retrospective nature and the relatively small sample of patients.

In conclusion, different data are available in the literature on whether antiviral treatment increases the chronicity of acute hepatitis B. In this study, it was found to increase chronicity. It was also observed that lamivudine decreased HBsAg seroconversion in patients with acute hepatitis B treated with lamivudine, whereas entecavir increased seroconversion. No studies with TDF could be identified. In this study, it was also found to reduce HBsAg seroconversion. Further prospective studies involving larger populations are needed on this field where different results have been obtained.

Conflict of interest

All authors declare that there is no conflict of interest.

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