Original Article

Comparison of First-year Results of Tenofovir and Entecavir Treatments of Nucleos(t)ide-naive Chronic Hepatitis B Patients with Hepatosteatosis

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ABSTRACT

Background/Aim: Hepatic steatosis may influence the response to antivirals in chronic hepatitis B patients. This study aimed to compare the efficacy of entecavir and tenofovir in nucleos(t) ide-naive chronic hepatitis B patients with hepatosteatosis during 48 weeks of therapy. **Patients and Methods:** We retrospectively reviewed our data for chronic hepatitis B patients. Nucleos(t) ide-naive patients with hepatosteatosis who took entecavir or tenofovir for at least 48 weeks were included. We compared entecavir and tenofovir after 48 weeks of therapy with respect to virological, biochemical, and serological responses in patients with hepatosteatosis. **Results:** Of the 63 patients, 21 received entecavir and 42 received tenofovir. Baseline characteristics of the patients were similar except for body mass index. At the end of week 48, there was no statistically significant difference between tenofovir and entecavir treatment regarding total HBV-DNA negativity and alanine transferase normalization in patients with chronic hepatitis B and hepatosteatosis. **Conclusions:** Entecavir and tenofovir are similarly effective in nucleos(t)ide-naive chronic hepatitis B patients with hepatosteatosis after 48 weeks of therapy.

Key Words: Entecavir, hepatitis B, hepatosteatosis, tenofovir

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Chronic hepatitis B (CHB) is an important cause of morbidity and mortality due to its life-threatening complications. Oral antivirals such as entecavir and tenofovir are drugs used successfully to treat CHB.[1,2] Nonalcoholic fatty liver disease (NAFLD) is comprised of a spectrum of clinical entities ranging from simple hepatosteatosis to steatohepatitis or cirrhosis. Based on epidemiological studies, NAFLD is estimated to occur in one-third of the general population in the United States and 25% in our region.[3] The risk of NAFLD increases with higher body mass index (BMI) and is usually regarded as the liver manifestation of metabolic syndrome.[4]

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Hepatosteatosis overlapping with CHB is present in 27%–51% of patients with HBV.[5-7] Although the source of steatosis in HBV patients remains to be clarified, some recent data show that steatosis is related to host metabolic factors such as BMI and metabolic syndrome rather than viral status (HBV-DNA, HBe antigen).[8,9] On the other hand, the impact of superimposed hepatosteatosis in patients with CHB is still not clearly defined. Jin *et al*. showed entecavir failure possibly linked to hepatosteatosis in a recent study with 200 patients.[9] Although hepatosteatosis has not been shown to decrease the response to antiviral treatment in chronic hepatitis B, it seems to worsen the prognosis of hepatic fibrosis in HBV.[10] In this study, we aimed to compare the first-year results of antiviral treatment of nucleos(t)ide-naive CHB patients with hepatosteatosis as a single-center experience.

PATIENTS AND METHODS

Patients

Sixty-three CHB patients with hepatosteatosis (32 males, 31 females) followed between 2011 and 2013 in our center

and treated with entecavir or tenofovir were investigated retrospectively. Patients' age was between 21 and 68 years. The mean age was 45.4 ± 12.7 years.

The patients were eligible for inclusion if they fulfilled the following criteria: Seropositive for HBsAg, elevation of serum alanine transferase (ALT) for at least 6 months, detectable serum HBV-DNA, HBeAg-negative, anti-HBe antibody positive, no evidence of features of decompensated cirrhosis including ascites, varices, portal hypertension, hepatocellular carcinoma, no evidence of other hepatotropic viruses (HCV, HDV), no previous treatment for HBV with either interferon or nucleoside analogs, normal creatinine clearance, at least one year of follow-up in our department, and absence of alcohol consumption. Hepatosteatosis was defined by moderate-to-severe steatosis in ultrasonography. Fatty infiltration of the liver is accepted as a diffuse increase in echogenicity (a bright liver, exceeding that of the renal cortex or spleen). Intrahepatic vessels are sharply demarcated, and posterior aspects of the liver are well depicted.[11] To prevent false-positive results, fatty liver was diagnosed if all of these criteria were fulfilled. Ultrasonography was performed by the same experienced radiologists. Ultrasonography shows steatosis with a sensitivity over 80% and a specificity over 90%.[12] Patients were not recommended to be on diet and exercise.

Liver biopsies were examined after staining with hematoxylin and eosin, Masson's trichrome, Reticulin silver stain, and Orcein. Liver histology was evaluated according to Ishak, which determines two major components, necroinflammation and fibrosis.[13] The liver inflammation score (between 0 and 18) is the sum of the piecemeal necrosis score (0–10), lobular inflammation score (0–4), and portal inflammation score (0–4). The fibrosis score was based on the degree and extent of fibrosis, between 0 and 4. Nonalcoholic steatosis (NAS) was determined as liver parenchymal involvement by steatosis as follows: <5% score 0, between 5%-33% score 1, between 33%–66% score 2, and >66% score 3.[14] Antiviral therapy, such as with potent antivirals including tenofovir and entecavir, was indicated if liver inflammation was ≥6, or liver fibrosis was ≥2.

Tenofovir (245 mg daily) or entecavir (0.5 mg daily) were initiated if the patient's HBV-DNA level was $\geq 1 \times 10^7$ copies/mL and liver biopsy showed necroinflammatory activity ≥6 or fibrosis stages 2–4. Antiviral choice for each patient was based on physician preference. All patients were followed every 4 weeks until week 48. Plasma samples were routinely assessed for hematological variables [complete blood count, ALT, aspartate transaminase (AST), bilirubin levels] every 4 weeks for documentation of any adverse events. The normal ranges of ALT and AST in our laboratory are 35 and 35 U/L, respectively. HBsAg, anti-HBs antibody, and HBV-DNA were assessed every 12 weeks. The primary efficacy endpoint at week 48 was HBV-DNA negativity. The secondary endpoint was ALT normalization.

Assays

Blood chemistry tests were done using an automated blood analyzer (Siemens Diagnostics, Bad Nauheim, Germany). Hepatitis B serology markers, that is, HBsAg, HBeAg, and anti-Hbe, were checked using enzyme-linked immunosorbent assay (ELISA) with commercial kits. Quantitative serum HBV-DNA levels were measured using the real-time PCR-based technique (COBAS® HBV Test, Roche Diagnostics, Basel, Switzerland). The lower detection limit was 15 IU/mL.

Statistical analysis

Characteristics of the study subjects are presented descriptively; continuous variables are expressed as mean ± standard deviation or median (range), whereas categorical variables are presented as frequency and percentage. The association between drugs and normalization of serum ALT, AST, and negativity of HBV-DNA levels were analyzed statistically. The mean comparisons were tested using the Pearson's Chi-square test and independent sample *t*-test. A P value of < 0.05 was considered significant. Statistical analysis was performed using the software Statistical Program for Social Studies version 16.0 for Windows PC (SPSS Inc, Chicago, IL, USA).

RESULTS

Demographic and baseline characteristics of the patients included in the study were similar between the tenofovir and entecavir groups, except for BMI [Table 1]. Liver steatosis severity determined by ultrasonography and liver histology were similar between tenofovir and entecavir groups [Table 1]. BMI was higher in the entecavir group with a statistical significance ($P < 0.034$), before and at week 48 of treatment [Tables 1 and 2]. There were no adverse events recorded during the study period.

Regarding HBV DNA negativity, there was no statistically significant difference between tenofovir and entecavir patients at weeks 12, 36, and 48. But at week 24, tenofovir was better with a statistical significance. Regarding ALT normalization, there was no statistically significant difference between tenofovir- and entecavir-treated patients at weeks 12, 24, 36, and 48. ALT normalization was achieved in 26.2% of patients on tenofovir and 14.2% of patients on entecavir treatment in the 12th week. At the end of 48 weeks, 88% of tenofovir and 85.7% of entecavir patients attained ALT normalization.

Table 1: Demographic profile and baseline characteristics of the patients

Variables	Tenofovir (*n*=42)	Entecavir (*n*=21)	*P*
Mean age (years)	45.3±14.2	45.±9.3	0.887
Male	22 (52.3%)	10 (47.6%)	0.722
Female	20 (47.7%)	11 (52.4%)	
HBV DNA			
Log10 copies/mL	$3.8\times10^7\pm1.5\times10^7$	$5.8\times10^7\pm4.3\times10^7$	0.665
ALT levels (IU/L)	85.5±48.8	101±62.7	0.310
AST levels (IU/L)	60.4±36.7	66±44.6	0.626
Bilirubin (mg/dL)	0.85±0.21	0.91±0.27	0.360
Body mass ındex (kg/m^2)	27.5±2.3	29.1±2.9	0.034
Steatosis (Ultrasonography)			
Grade 1	19 (45.2%)	6 (28.6%)	0.442
Grade 2	15 (35.7%)	10 (47.6%)	
Grade 3	8 (19%)	5 (23.8%)	
Steatosis score (liver histology)			
Score 1	5 (11.9%)	5 (23.8%)	
Score 2	21 (50%)	10 (47.6%)	
Score 3	16 (38.1%)	6 (28.6%)	0.443
Histological activity ındex (HAI)			
HAI 5-7	23 (54.7%)	12 (57,2%)	0.917
HAI≥8	19 (45.3%)	9 (42.8%)	
Fibrosis (ISHAK)			
1	5 (11.9%)	6 (28.6%)	0.163
2	23 (54.8%)	8 (38.1%)	
3	12 (28.6%)	4 (19%)	
4	2 (4.8%)	3 (14.3%)	

ALT: Alanine transferase; AST: Aspartate transferase

Table 2: Biochemical and virological responses

Variables	Tenofovir *N*=42	Entecavir *N*=21	*P*
At week 12 (%)			
ALT normalization	11 (26.2%)	3 (14.2%)	>0.795
HBV-DNA negativity	1 (2.4%)	0 (0%)	>0.476
At week 24 (%)			
ALT normalization	25 (59.5%)	7 (33.3%)	>0.433
HBV-DNA negativity	9 (22%)	0 (0%)	<0.020
At week 36 (%)			
ALT normalization	38 (90.4%)	14 (66.6%)	>0.187
HBV-DNA negativity	14 (42.4%)	11 (52.4%)	>0.474
At week 48			
ALT normalization	37 (88%)	18 (85.7%)	>0.997
HBV-DNA negativity	12 (63.2%)	6 (60%)	>0.868
Total HBV-DNA negativity	36 (83.3%)	17 (81%)	>0.814
Total ALT normalization	38 (90.5%)	18 (85.7%)	>0.571
BMI (kg/m^2)	27.4±2.2	29±2.7	<0.029

ALT: Alanine transferase; BMI: Body mass index

DISCUSSION

The aim of antiviral therapy of CHB is to prevent long-term complications of CHB, such as cirrhosis. To attain this goal, persistent suppression of HBV is necessary. The current antivirals effectively suppress viral replication. Tenofovir provides more than 81% of HBV-DNA negativity.[15] Entecavir has comparable results to tenofovir. Entecavir suppresses serum HBV-DNA to undetectable levels in 75% of patients after 48 weeks.[16] However, CHB overlapping hepatosteatosis is still a matter of debate regarding the efficacy of antivirals. Hepatosteatosis was previously reported to be associated with entecavir failure in those patients.[10] Cellular fat accumulation was claimed to decrease the contact area between the drugs and hepatocytes, causing reduced bioavailability of entecavir or tenofovir.[17] Also, a decrease in cytochrome enzyme activity may diminish the activity of the drugs.[18] In the present study, there were no statistically significant differences between tenofovir and entecavir in HBV-DNA suppression to undetectable levels at week 48. When comparing the response rates overall in the patients, our results can be interpreted as entecavir and tenofovir treatment being equally effective in CHB patients with hepatosteatosis. Nevertheless, this result needs to be confirmed with new broad-based prospective studies in patients with hepatosteatosis. Similarly, in the normalization of liver enzymes, there was no statistically significant difference between entecavir and tenofovir groups. Meanwhile, we should emphasize that the pre-treatment and week 48 BMI of patients who received entecavir were higher than those of patients who received tenofovir, with a statistically significant difference [Tables 1 and 2]. In fact, the rates of ALT normalization in our study patients with hepatosteatosis were similar to the expected current rates for those drugs, so it can be suggested that hepatosteatosis does not mask the ALT normalization in CHB patients with hepatosteatosis. New studies are necessary to confirm this observation. BMI values at pretreatment and week 48 were similar for each drug group in this study, meaning that the conditions that are associated with fatty liver such as obesity did not change during antiviral treatment. However, lack of a detailed analysis of metabolic factors such as insulin, leptin, and insulin resistance scores is a limitation of the present study. There are some other limitations of this study. First is that a longer follow-up period (2 or 3 years) and a larger sample size would be better. The other limitation is the lack of demonstration of a histological activity improvement at the 48th week. Genotypes were not analyzed; however, most patients with CHB in Turkey have genotype D, and genotype is not normally determined for naive CHB patients. We used both liver biopsy and hepatic ultrasonography for determining hepatic steatosis. All patients with hepatitis B

may not have a liver biopsy specimen due to contraindicated conditions. Thus, a noninvasive imaging modality such as hepatic ultrasound has shown a sensitivity over 80% and a specificity over 90% in detecting steatosis.[12] Also, hepatic ultrasound is more practical, comfortable, less expensive, and the most convenient modality compared with liver biopsy in clinical practice, as was done in our study.[19] The other issue is that we only included Turkish patients in the study and our results need verification in other ethnic groups. In a recent study,[9] entecavir resistance was not observed and hepatic steatosis was shown to be associated with entecavir treatment failure. These conflicting results may come from the different ethnicities, genotypes of hepatitis B, and criteria for starting antiviral therapy. We did not observe entecavir resistance in our study, which may be due to the short observation period and the insufficient number of patients in the study.

In conclusion, entecavir and tenofovir were similarly effective in nucleos(t)ide-naive CHB patients with hepatosteatosis.

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