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

Zeynal Dogan, Levent Filik, Bilal Ergül, Murat Sarikaya

Department of Gastroenterology, Ankara Education and Research Hospital, Altındağ, Ankara, Turkey

Address for correspondence: Dr. Zeynal Doğan, Department of Gastroenterology, Ankara Education and Research Hospital, Ulucanlar Street, District Sukriye, Altındağ, Ankara - 06230, Turkey. E-mail: doganzeynal@yahoo.com

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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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 ≥1×10^7 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.
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

### 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±19.3        | 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±10^4±1.5^10^  | 5.8±10^4±4.3^10^ | 0.665|
| ALT levels (IU/L)            | 85.5±48.8        | 101±62.7         | 0.310|
| AST levels (IU/L)            | 60±36.7          | 66±44.6          | 0.626|
| Bilirubin (mg/dL)            | 0.85±0.21        | 0.91±0.27        | 0.360|
| Body mass index (kg/m²)      | 27.5±2.3         | 29.1±2.9         | 0.034|

### Table 2: Biochemical and virological responses

| Variables                    | Tenofovir     | Entecavir     | 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/m²)                  | 27.4±2.2      | 29±2.7        | <0.029|

ALT: Alanine transferase; AST: Aspartate transferase; BMI: Body mass index.
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In conclusion, entecavir and tenofovir were similarly effective in nucleos(t)ide-naive CHB patients with hepatosteatosis.

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