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ORIGINAL ARTICLE

A long-term multicenter study: Entecavir versus Tenofovir in treatment of nucleos(t)ide analogue-naive chronic hepatitis B patients

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KEYWORDS
Entecavir versus Tenofovir;
Chronic Hepatitis B (CHB);
Hepatitis B Virus (HBV);
Efficacy;
Predictors of response

Summary
Background: Entecavir (ETV) and tenofovir disoproxil fumarat (TDF) are the two first-line therapies recommended in the treatment of chronic hepatitis B because of having potent antiviral effect and high genetic barriers against resistance. We aimed to compare efficacy of these drugs and to evaluate predictors of viral suppression.
Methods: This multicenter retrospective study was conducted in nucleos(t)ide analogue-naive chronic hepatitis B (CHB) patients from different 6 centers.
Results: Of the 252 patients, 166 received ETV and 86 TDF. The two groups were similar in terms of age, gender, baseline ALT levels and fibrosis scores. ETV had significantly higher baseline HBV DNA, histological activity index and lower hepatitis B early antigen (HBeAg) seropositivity.

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Treatment duration was longer in ETV group ($P < 0.001$). In univariate analysis, undetectable HBV DNA and ALT normalization rates were detected significantly higher in ETV groups ($P < 0.001$ and 0.049, respectively). There was no significant difference between groups in terms of HBeAg seroconversion, virological breakthrough, time to virological breakthrough and time to ALT normalization. Entecavir was more effective in reducing HBV DNA levels at the 3rd, 6th and 12th months of the treatment ($P = 0.06$, 0.021 and 0.012, respectively). However, multivariate Cox regression analysis indicated that TDF therapy compared to ETV had an increased probability of achieving complete viral suppression (HR = 1, 66; 95% CI 1.21—2.33; $P = 0.010$). Hepatitis B surface antigen (HBsAg) seroconversion was occurred in only one patient in ETV group.
Conclusion: ETV leads to an early response on HBV DNA decline in the first year of the treatment. However, TDF is more successful than entecavir in achieving virological suppression.

Introduction

Chronic hepatitis B (CHB) is one of the major causes of chronic liver diseases worldwide. High level of hepatitis B virus (HBV) DNA is the initiator factor of disease progression [1—3]. The suppression of HBV DNA replication is correlated with clinical and histological improvements [4]. In clinical practice guidelines, serum HBV DNA level is used for the decision to begin of antiviral treatment and monitoring of response to therapy in CHB patients [1,2].

The primary endpoints for treatment of CHB are complete virological suppression, hepatitis B early antigen (HBeAg) clearance and seroconversion (in HBeAg-positive patients), the loss of hepatitis B surface antigen (HBsAg) and the development of antiHBs antibody [5—7]. The loss of HBsAg is the only endpoint providing discontinuing of antiviral agent, but rarely achieved [1]. HBeAg seroconversion is accompanied with the decline of serum HBV DNA, but available in only HBeAg positive CHB. Therefore, the primary goal of CHB treatment is effectively suppressing of HBV replication and thereby reducing hepatic necroinflammation and preventing cirrhosis and hepatocellular carcinoma (HCC) [1—3].

Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are recommended as the first-line therapies in current clinical practice guidelines because of having potent antiviral effect and high genetic barriers against resistance [3]. To date, no or very low resistance rate were reported in the long-term use of these agents [8,9]. This provides an advantage for CHB infection that requiring long-term treatment and they can be confidently used as the fist-line therapy.

ETV has been commercially available since 2005 and TDF since 2008. The increased HBV DNA suppression and higher HBeAg seroconversion rates with both ETV and TDF treatment have been reported [7]. However, there are limited studies comparing ETV and TDF conducted in a large number of patients. The aim of this study is to compare effectiveness of ETV and TDF in a large patient population.

Methods

We conducted a retrospective multicenter cohort study comparing the efficacy of ETV and TDF in the treatment of nucleos(t)id naïve CHB infection. The adult patients treated with ETV and TDF at the Department of Infectious Disease and Clinical Microbiology of six different centers (three university hospitals and three education and research hospitals) around Turkey between June 2008 and June 2014 were evaluated retrospectively.

The inclusion criteria are HBsAg positivity for at least six months, oral antiviral therapy naïve, both positive and negative serology for HBeAg, pretreatment DNA level $\geq 2 \times 4$ log10 IU/mL, therapy with ETV 0.5—1 mg/day or TDF 245 mg/day for at least six months, a regular monitoring of serum DNA level by PCR every three months for the first year of treatment and every six months after that.

The patients younger than 18 years old, co-infected with hepatitis C, hepatitis D or human immunodeficiency virus, immunosuppressed, treated with oral antivirals previously, complicated with cirrhosis, hepatic decompensation or HCC at the beginning of treatment, having no regular records were excluded.

Demographical, biochemical, serological and treatment data of the patients were recorded in an individual patients form. The following parameters were recorded in detailed: age, gender, weight, baseline ALT and HBV DNA level, HBeAg status, histological activity index (HAI) and fibrosis through Ishak score in pretreatment liver biopsy, ALT and HBV DNA level at the 3rd, 6th, 9th and 12th at the first year of the treatment and every six months in the following years, time to undetectable HBV DNA, ALT normalization, HBeAg seroconversion (in HBeAg positive patients) and virological breakthrough, total duration of treatment. The biochemical, serological and virological response of the patients in ETV and TDF groups were analyzed. HBV DNA decline over time and cumulative probability of virological response by ETV and TDF therapy were compared. The independent predictors for complete viral suppression were evaluated with survival analysis. The primary endpoint was to achieve a complete viral suppression; secondary endpoint was the achieving of serological and/or biochemical response in both treatment groups.

A complete virological response was defined as undetectable HBV DNA level in serum. The lower limit for undetectable HBV DNA was determined as below ≤ 20 IU/mL or 100 copies/mL by PCR assays. ALT levels greater than 40 IU/L in serum was defined as a high ALT level. The decline of high ALT levels to the normal range was defined as biochemical response. The serological response was defined as the loss of HBeAg and/or emergence of anti-HBe during the treatment.

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