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Original Article

On-treatment HBV DNA level could predict HBeAg seroclearance in patients with HBeAg-positive chronic hepatitis B with entecavir therapy

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Abstract

Background: Hepatitis B e antigen (HBeAg) status is associated with clinical outcomes, and seroconversion of HBeAg is one of the treatment goals. In this study, we determined the association of on-treatment serum hepatitis B virus (HBV) DNA levels in HBeAg-positive chronic hepatitis B patients who were receiving entecavir (ETV) treatment.

Methods: A retrospective cohort study was conducted involving 135 (78 male and 57 female; mean age, 42.3 ± 13 years) patients with HBeAg-positive chronic hepatitis B (CHB). Between August 2008 and March 2014, each patient was treated with ETV for at least 96 weeks, and their HBV DNA levels were evaluated every 3−6 months. HBeAg seroclearance at the 96th week was defined as an absence of serum HBeAg within 96 weeks after ETV treatment. Univariate and multivariate logistic regression analysis was used to identify the predictors of 96th week HBeAg seroclearance, and a multivariable model was constructed.

Results: Among the 135 ETV-treated HBeAg-positive CHB patients, 37 patients achieved HBeAg seroclearance (Group 1), whereas 98 patients had persistent HBeAg-positive status (Group 2) at the 96th week check-up. The baseline laboratory data was not significantly different between both the two groups. At the 24th and 48th weeks, there were significant differences between Group 1 and Group 2 in the percentage of patients with HBV DNA levels < 20 IU/mL [17/77 (22.1%) and 11/23 (47.8%), $p = 0.032$; 45/89 (50.6%) and 26/35 (74.3%), $p = 0.028$, respectively).

Conclusion: Our study demonstrated that HBV DNA levels < 20 IU/mL at the 24th and 48th weeks could predict serum HBeAg loss in ETV-treated HBeAg-positive patients with CHB.

Keywords: entecavir; hepatitis B e antigen; hepatitis B virus; hepatitis B virus DNA; seroclearance

1. Introduction

Chronic hepatitis B (CHB) is a worldwide public health burden. CHB infection has been associated with an increased risk for developing cirrhosis and hepatocellular carcinoma.[1] In recent decades, there has been a dramatic and rapid progress in the treatment of CHB.[2,3] The current treatment for CHB includes interferon-alfa, lamivudine, adefovir, entecavir (ETV), telbivudine, tenofovir, and pegylated interferon-a2a. There is evidence supporting the concept that antiviral therapy can ameliorate liver damage, progression of cirrhosis, and incidence of hepatocellular carcinoma.[4−6]

In patients with CHB infection, hepatitis B e antigen (HBeAg) is initially positive and accompanied by high levels of hepatitis B virus (HBV) DNA, which may persist for years or even decades.[7] HBeAg-positive immunotolerant patients with significant horizontal and vertical transmission carry a risk of contracting active chronic hepatitis and its complications. The current treatment options are not optimal. Pegylated interferon therapy offers sustained off-treatment responses in

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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only a minority of patients.[8] Nucleoside analogs can suppress the on-treatment HBV DNA, improve liver histological lesions, reverse cirrhosis in the majority of cases, and improve survival rates.[9,10] Antiviral therapies may lead to sustained responses during therapy until the onset of treatment withdrawal. Thus, more commonly, a therapy must be continued to maintain responses achieved during the therapy. The short-term goal of treatment for HBeAg-positive CHB is to achieve an initial response by HBeAg loss or seroconversion and/or HBV DNA suppression, alanine aminotransferase (ALT) normalization, and prevention of hepatic decompensation.[11,12]

HBV DNA levels are associated with clinically significant pathological events, such as cirrhosis; therefore, changes in the serum levels of HBV DNA could determine a risk for hepatocellular carcinoma.[13,14] For on-treatment follow-up, HBeAg loss/seroconversion is important during the nucleoside therapy for CHB patients. In China and other East Asian countries, HBeAg seroconversion was achieved in approximately 44−47% of patients after 4−5 years of lamivudine-based treatment.[15,16] Under lamivudine treatment, studies from several Taiwan reports indicated that the rate of HBeAg seroconversion was associated with the pretreatment ALT level.[17,18]

ETV, a new guanosine nucleoside analog with specific activity against HBV DNA polymerase, represents a third agent within the nucleoside/nucleotide HBV polymerase inhibitor class. Compared with lamivudine and adefovir, ETV at 0.5 mg daily reportedly induces greater HBV DNA suppression, with HBV DNA becoming undetectable in 60−71% of HBeAg-positive patients and 88−90% of HBeAg-negative patients at 48−52 weeks.[3,19] The HBeAg seroconversion rate was 31% by 2nd year, and the HBeAg seroconversion rate in 141 HBeAg-positive patients was 23% from 96th week to 240th week.[12] Among patients treated with ETV at 0.5 mg daily, 83−90% patients had undetectable HBV DNA, and 24−44% patients had HBeAg seroconversion at 3rd year of the treatment.[20−22]

ETV could suppress HBV DNA effectively, but the dynamic change of HBV DNA and corresponding HBeAg changes have not yet been clearly elucidated. Whether on-treatment follow-up HBV DNA is capable of predicting HBeAg seroconversion or seroclearance requires further investigation. To address these concerns, we conducted the present study to investigate whether on-treatment serum HBV DNA levels could predict HBeAg seroclearance during ETV-based therapy for HBeAg-positive CHB patients. In this retrospective, study patients were followed-up regularly every 12 weeks. Follow-ups included evaluations of serum HBV DNA levels at the 12th week, 24th week, and 48th week since the ETV treatment initiation. The results of our study provide important information with respect to the prediction of HBeAg seroclearance during ETV therapy among HBeAg-positive CHB patients.

2. Methods

2.1. Patients

We conducted a retrospective cohort study by reviewing medical records and underwent a routine, regular treatment protocol for CHB patients. Between August 2008 and March 2014, a total of 135 (78 male and 57 female; mean age, 42.3 ± 13 years) patients with HBeAg-positive CHB who were treated with ETV for at least 96 weeks were included in this study. Patients were followed-up every 3 months and ALT, HBV DNA, and HBeAg status were routinely assessed every 3−6 months at Taichung Veterans General Hospital. Virological response is defined as a serum level of HBV DNA of < 20 IU/mL.[23]

Patients were excluded in case of the following: (1) they had previously undergone antiviral treatment for hepatitis B; (2) they had HBeAg seroclearance within 24 weeks after ETV treatment; and (3) they were coinfected with the hepatitis C virus, hepatitis D virus, or human immunodeficiency virus (HIV). The study was approved by the Institutional Review Board of our institution (VGHTC CE16037B).

2.2. Outcome measurements

The primary endpoint of our analysis was HBeAg seroclearance, which was defined as negative serum HBeAg levels within 96 weeks of ETV treatment. ALT, bilirubin and HBV DNA levels were also routinely evaluated in our department.

2.3. Laboratory methods

HBV DNA was determined by real-time PCR assay (Roche Cobas TaqMan HBV Test). Hepatitis B surface antigen (HBsAg) and HBeAg and anti-HBe were determined by electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany).

2.4. Statistical analysis

Statistical tests were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using the Chi-square test and Fisher's test, and continuous variables were expressed as mean and range and compared using the Student's t test or Mann−Whitney U test. Logistic regression was performed to analyze factors associated with HBeAg seroclearance at the 96th week, and significant factors ($p < 0.05$) in the univariate analysis were subjected to multivariate analysis to determine independent predictive factors. To avoid co-linearity of both parameters, HBV DNA levels at 24th week and 48th week were analyzed individually in multivariate analysis with age and sex adjustment. Statistical significance was defined as a p value of < 0.05.

3. Results

3.1. Patients' characteristics

Demographic data of ETV-treated patients with HBeAg seroclearance and without HBeAg seroclearance within 96 weeks is shown in Table 1. A total of 135 HBeAg-positive CHB patients received ETV treatment. There were 37