The Brazilian Journal of
INFECTIOUS DISEASES

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Original article

Predictors of HBeAg seroconversion after long-term nucleos(t)ide analogues treatment for chronic hepatitis B: a multicenter study in real clinical setting

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ARTICLE INFO

Article history:
Received 16 November 2015
Accepted 10 March 2017
Available online 27 March 2017

Keywords:
Chronic hepatitis B
Hepatitis B and antigens
Nucleos(t)ide analogue
Adherence

ABSTRACT

Aims: To evaluate the HBeAg seroconversion rate in real clinical setting and explore its predictors in long-term nucleos(t)ide analogues (NAs) treatment for chronic hepatitis B (CHB).
Methods: 251 patients were recruited from January 2001 to September 2009 in four hospitals in Hebei province, China, for this retrospective study. Clinical and laboratory data before and after treatment with lamivudine (LAM, 100 mg daily), adefovir (ADV, 10 mg daily), telbivudine (LDT, 600 mg daily), entecavir (ETV, 0.5 mg daily), and LAM/ADV combination were compared among three groups according to treatment outcomes: synchronous HBeAg loss and HBeAg seroconversion, anti-HBe development after treatment, and no anti-HBe. Adherence was also evaluated.
Results: In real clinical setting, cumulative HBeAg seroconversion rates were 14.3%, 32.7%, 43.0%, 46.9%, and 50.5% after 1, 2, 3, 5, and 8 years, respectively. 45 patients (17.9%) were non-adherent. Adherence ($p < 0.001$, Hazard Ratio (HR) = 2.203), elevated alanine aminotransferase (ALT) levels ($p < 0.001$, HR = 2.049), and non-vertical transmission ($p = 0.006$, HR = 1.656) were predictors of HBeAg seroconversion.
Conclusion: Adherence, elevated ALT, and non-vertical transmission are predictors of HBeAg seroconversion in CHB patients treated with NAs.

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http://dx.doi.org/10.1016/j.bjid.2017.03.001

Introduction

Chronic hepatitis B (CHB) remains a major public health concern, because of worldwide prevalence and the potential to cause adverse consequences such as liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC).[1] However, CHB can be managed with effective antiviral agents. Hepatitis Be antigen (HBeAg) seroconversion is considered the treatment endpoint in HBeAg-positive patients.[2] It is correlated with clinical remission accompanied by improved necro-inflammatory activity,[3] fibrosis regression,[4] lower risk of liver cirrhosis and HCC,[5] and higher incidence of complication-free survival.[6]

Nucleos(t)ide analogues (NAs) are recommended as first-line anti-HBV agents owing to high antiviral potency, ease of use, and high tolerability in HBeAg-positive patients, especially those with high hepatitis B virus (HBV) DNA loads and liver cirrhosis. However, HBeAg seroconversion rates after treatment with five commonly prescribed oral antiviral agents are 12–23% after one year of treatment, 25–31% after two years, and up to 44% after three years according to recent clinical trials.[7] In addition, two recent studies conducted in the United States revealed that HBeAg seroconversion rate is significantly lower in real clinical setting, especially in entecavir (ETV)-treated patients.[8,9] HBeAg seroconversion rate in actual clinical setting was less than 10% during the first year of NAs therapy. A number of factors, such as older age, higher alanine aminotransferase (ALT) levels, lower HBV DNA load, genotype B (*vs.* C), and pathological factors, may predispose patients to HBeAg seroconversion either in the natural course or during individual NAs or interferon (IFN) therapies.[10–13] However, few studies have evaluated HBeAg seroconversion rates during long-term NAs therapy in real clinical setting, but not assessing factors that may predict HBeAg seroconversion.

Currently, adherence studies mainly focus on anti-HIV therapies, and many options have been tested for adherence assessment, including visual analogue scale and the so-called 3-day recall instrument.[14,15] Although such studies are less common in the HBV field, it was demonstrated that higher adherence to NAs treatment in CHB patients tended to result in decreased rate of viral breakthroughs.[16]

Thus, the goal of the current study was to evaluate long-term outcomes of NAs treatment through HBeAg seroconversion rates, whose predictive factors were also assessed, in a multicenter set of CHB treatment-naive patients in real clinic in China.

Materials and methods

Study design and patient population

This was a retrospective case control study of consecutive treatment-naïve CHB patients treated with lamivudine (LAM, 100 mg daily), adefovir (ADV, 10 mg daily), telbivudine (LDT, 600 mg daily), ETV (0.5 mg daily), and LAM and ADV combination for more than three years from January 2001 to September 2009 at five departments of gastroenterology and hepatology in Chinese hospitals.

A total of 1591 patients were enrolled. Inclusion criteria were: ≥18 years of age, no previous HBV treatment, and detectable HBeAg and negative anti-HBe at baseline. Patients were excluded if there was any evidence of autoimmune hepatitis, metabolic liver diseases, heavy alcohol abuse, hepatitis C virus, hepatitis D virus, hepatitis E virus, human immunodeficiency virus (HIV), recent exposure to hepatotoxic drugs, and pregnancy for women. Patients with changed anti-HBV agents (switching to an alternate NAs monotherapy, IFN therapy, or adding another anti-HBV medication) were also excluded. A total of 251 patients were finally included in the study but only 177 were fully assessed with recorded HBeAg loss. Patient clinical records, including laboratory results and adherence reports, were reviewed using a self-report questionnaire.

Laboratory examinations were generally conducted at baseline and at 12–24 week intervals. Serum levels of ALT, alpha fetoprotein (AFP), HBV DNA, HBeAg, anti-HBe, HBsAg, and anti-HBs were evaluated. Serum HBV DNA load in CHB patients was detected by real time polymerase chain reaction (PCR) in our Hospital, and detection limits were 500 and 10^8 copies/mL, for lower and upper levels, respectively. HBeAg and HBsAg were measured quantitatively or qualitatively (described as "positive" or "negative").

The study protocol was approved by the Ethics Committee of our Hospital, and the requirement for written informed consent was waived.

Assessment of treatment outcomes

In this study, HBeAg seroconversion was defined as loss of HBeAg with the development of anti-HBe, accompanied with complete viral suppression (undetectable levels of HBV DNA replication, <500 copies/mL) and normalization of ALT (<40 IU/L).

Adherence measurement

Three questions regarding adherence to anti-HBV NAs were included in a self-administered questionnaire at the last follow-up. The first two were adapted from the questionnaire established for HIV-infected patients by the AIDS Clinical Trial Group.[14] The third question corresponded to a visual analogue scale (VAS)[15] (Table 1).

Patients were classified as fully adherent if skipping no more than one medication dose, with a VAS score of 10. Other patients were classified in the non-adherence group. This approach tends to minimize adherence inflation using self-reporting to healthcare providers.[16]

Statistical analysis

Descriptive statistics were reported as number and percentage (%) for categorical variables, and mean ± SD or median (range) for continuous variables. Groups of patients with different NAs and HBeAg seroconversion status were compared by χ^2-test, log-rank test, Student's *t*-test, and one-way analysis of variance (ANOVA) for categorical and continuous variables, respectively. Kaplan–Meier analysis was used to assess cumulative incidence rates over time. Cox proportional hazard regression analysis was used to identify independent