Predictive Factors for Sustained Remission after Discontinuation of Antiviral Therapy in Patients with HBeAg-positive Chronic Hepatitis B

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Background/Aims: The optimal timing for discontinuing oral antiviral therapy in patients with HBeAg-positive chronic hepatitis B (CHB) is unclear. The aim of our study was to investigate sustained remission after stopping antiviral therapy in patients with HBeAg-positive CHB.

Methods: We analyzed the medical records of 58 patients who were HBeAg-positive and had discontinued antiviral therapy. Antiviral therapy was discontinued after HBeAg seroconversion and HBV DNA negativity for 6-12 months with consolidation therapy. Virologic relapse was defined as an increase in serum HBV DNA >2,000 IU/mL.

Results: No difference was observed between the virologic non-relapse and virologic relapse groups in baseline HBV DNA level (p=0.441) or duration of seroconversion (p=0.070). Time-to-undetectable HBV DNA during treatment was shorter in the virologic non-relapse group (29 patients) compared to the relapse group (29 patients) (4.9±2.6 vs. 13.2±12.7 months; p<0.01). Cumulative relapse rates were 12.7% in month 3, 32.7% in month 6, 47.3% in month 12, and 52.7% in month 18. We determined by multivariate analysis that the consolidation period (≥18 months, p=0.020) and early virologic response (HBV DNA <20 IU/mL) at six months during antiviral therapy (p=0.017) were significant predictors for sustained remission.

Conclusions: A consolidation period of at least 18 months and early virological response at six months during antiviral therapy were associated with sustained remission in patients with HBeAg-positive CHB after treatment. (Korean J Gastroenterol 2016;67:28-34)

Key Words: Treatment; Chronic hepatitis B; Discontinuation; Remission; Relapse

INTRODUCTION

HBV is an important contributor to liver disease, and chronic HBV infection can cause cirrhosis and hepatocellular carcinoma (HCC).

Antiviral therapy with nucleos(t)ides (NAs) is effective in suppressing viral replication to normalize liver enzymes in patients with chronic HBV infection. However, virologic relapse often occurs after treatment, necessitating long-term antiviral therapy in such patients. Long-term treatment entails considerable financial burden on national...
health care systems.\textsuperscript{4,5} Because the optimal time to discontinue antiviral drug therapy is unclear, it is difficult to formulate a plan for discontinuation of oral NA antiviral therapy, needed to save cost and improve patient compliance.

In patients with HBeAg-positive chronic hepatitis B (CHB), current clinical practice guidelines suggest that treatment can be stopped after HBeAg seroconversion and an additional six to twelve months of consolidation therapy.\textsuperscript{6,7} The Asian Pacific Association for the Study of the Liver (APASL) guidelines recommend that treatment should be continued until the patient has achieved HBeAg seroconversion and undetectable serum HBV DNA with at least six months of additional treatment after the appearance of anti-HBe.\textsuperscript{6}

The durability of virologic non-relapse after treatment discontinuation appears to be low in patients with HBeAg-positive CHB. Patients experience high virological relapse rates after treatment, even when following the current recommendations.\textsuperscript{8-12} In a Korean study, younger age, lower bilirubin, and a longer consolidation period were predictive of sustained remission.\textsuperscript{8} Liang et al.\textsuperscript{10} reported that serum HBsAg levels at the end of treatment and rate of HBV DNA suppression are important for determining the appropriate time to stop antiviral drug treatment. The level and kinetics of HBsAg have recently emerged as useful tools for predicting virologic response and relapse after treatment discontinuation.\textsuperscript{10,13,14} However, the factors associated with virologic relapse have not been assessed. To improve the sustained remission rate in patients with CHB, more stringent criteria are needed to update practice guidelines.

The aim of this study was to investigate the factors predicting sustained remission after stopping antiviral therapy in patients with HBeAg-positive CHB.

**SUBJECTS AND METHODS**

1. **Patients**

We analyzed the medical records of patients who were HBeAg-positive and had discontinued antiviral therapy from March 2008 to December 2013 at Soonchunhyang University Hospitals in Cheonan, Seoul, and Bucheon, and at Gangneung Asan Hospital, Korea. We selected as study subjects patients who had discontinued antiviral therapy following HBeAg seroconversion and maintained undetectable HBV DNA for at least six months, as recommended by the APASL in 2008. We also required posttreatment care for at least 12 months, and analyzed until 24 months maximum. All patients had serum HBV DNA, serologic hepatitis B markers, and liver biochemical tests every three to six months. We excluded patients who were infected concurrently with hepatitis C, hepatitis D, or human immunodeficiency viruses, were exposed to hepatotoxic drugs, consumed a significant amount of alcohol, or underwent interferon or immunosuppressive therapy. No patients had liver cirrhosis, HCC, or any other malignancy.

Virologic response was defined as undetectable HBV DNA in serum using a sensitive PCR assay.\textsuperscript{6} Patients with an HBV load over 2,000 IU/mL after treatment discontinuation were characterized as having virologic relapse.\textsuperscript{15} Biochemical relapse was defined as return to an ALT level in serum more than twofold the upper limit of normal.\textsuperscript{6} The primary outcome was virologic relapse after cessation of antiviral therapy. This study was approved by the Investigation and Ethics Committee for Human Research at Soonchunhyang University Medical Center (Cheonan, Seoul, and Bucheon Hospital) and Ulsan University Medical Center (Gangneung Asan Hospital), and informed consent in writing was obtained from each patient in the study.

2. **Laboratory methods**

Serum HBV DNA was quantified using with the COBAS AmpliPrep-COBAS TaqMan HBV test (CAP-CTM; Roche Molecular Systems, Inc., Branchburg, NJ, USA), with a lower limit of detection of 20 IU/mL. Serum hepatitis markers including HBsAg, anti-HBs, HBeAg, and anti-HBe were detected using commercially available microparticle enzyme immunoassays (Abbott, Wiesbaden, Germany). Lamivudine-resistant mutations were identified using second-generation INNO-LiPA HBV DR v2 (Innogenetics NV, Ghent, Belgium).

3. **Statistics**

Statistical analysis was performed using SPSS (version 14.0; SPSS, Inc., Chicago, IL, USA). Continuous variables were expressed as means with standard deviation or medians with range, and categorical variables were expressed as a proportion. Student’s t-test and Mann-Whitney U-test or $\chi^2$ test and Fisher’s exact test were used to make comparisons between the sustained remission and relapse groups. The cumulative relapse rate was calculated by the