# Long-term outcomes after nucleos(t)ide analogue discontinuation in HBeAg-positive chronic hepatitis B patients

**D. He[1,2], S. Guo[1], P. Zhu[1], S. Tao[1], M. Li[1], H. Huang[1], J. Wang[1], Y. Wang[1] and M. Ding[2]**

1) *Institute of Infectious Diseases, Southwest Hospital, Third Military Medical University, Chongqing, and* 2) *Liver Disease Diagnoses and Therapy Center, The 88th Hospital of the Chinese PLA, Tai'an, China*

## Abstract

Nucleos(t)ide analogue (NUC) resistance is an important clinical risk resulting from long-term therapy in chronic hepatitis B (CHB) management. Discontinuation of NUCs is a feasible strategy to reduce resistance. We aimed to observe the outcomes after NUC withdrawal in HBeAg-positive CHB patients. A total of 97 patients (11 patients with HBsAg loss and 86 patients with sustained HBeAg seroconversion) were enrolled. HBV DNA levels and alanine aminotransferase (ALT) levels were monitored regularly after discontinuation. Relapse was defined as HBV DNA levels >2000 IU/mL in at least two determinations more than 4 weeks apart. HBeAg seroconversion was achieved within 48 weeks (interquartile range (IQR), 24–72 weeks). The time on consolidation therapy was 96 weeks (IQR, 84–144 weeks). No relapses occurred for HBsAg loss patients. Evidence of relapse was observed in 9.3% of HBeAg seroconversion patients. All relapse cases occurred within 48 weeks after discontinuation. The time to relapse was 33 ± 15 weeks. Elevation of HBV DNA and ALT levels over baseline were only observed in 12.5% of relapse patients. There were no significant differences in baseline characteristics (sex, HBV genotype, age or ALT levels) or time on consolidation therapy between patients with relapse or sustained response. NUC discontinuation in HBeAg-positive CHB patients is feasible after achieving HBeAg seroconversion at a minimum of 24 weeks. There is further benefit to prolonging the time on consolidation therapy to reduce relapse. More than 48 weeks of sustained response is a predictive marker for long-term sustained response.

**Keywords:** Chronic hepatitis B, discontinuation, HBeAg-positive, nucleos(t)ide analogues, relapse
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**Corresponding author:** Y. Wang, Gaotanyan Main Street 30, Shapingba District, Chongqing 400038, China
**E-mail: wym417@163.com**

## Introduction

About 350–400 million people worldwide live with chronic hepatitis B virus (HBV) infection. Approximately 25% of adults with chronic HBV infection since childhood later die from end-stage liver disease [1]. Therefore, the goal of chronic hepatitis B (CHB) therapy is to achieve sustained suppression of HBV replication. Nucleos(t)ide analogues (NUCs), including lamivudine, adefovir, entecavir, telbivudine and tenofovir, are generally administered for a long duration, as long as 5–6 years or more, until specific endpoints are achieved, even though HBV DNA levels can be suppressed until they are undetectable in a much shorter period of time [2].

Chronic hepatitis B may present either as hepatitis B e antigen (HBeAg) positive or HBeAg negative. HBeAg-positive CHB is characteristic of immune activation [2]. The ideal endpoint of therapy is sustained loss of hepatitis B surface antigen (HBsAg) with or without seroconversion to anti-HBs. However, the annual rate of HBsAg loss is only 0.5–2.3% [3–6], whilst loss of HBsAg rates after 1 year were 1% with lamivudine, 0 with adefovir, 2% with entecavir, 0 with telbivudine and 3% with tenofovir. Durable HBeAg seroconversion is a satisfactory endpoint because of its association with improved prognosis. HBeAg seroconversion rates are *c.*

20% for NUCs, increase with continued NUC treatment and are affected if resistance occurs [2]. Viral relapse and exacerbations of hepatitis may occur following discontinuation of NUC therapy, even for patients who develop HBeAg seroconversion [1]. Therefore, the decision to continue therapy after achieving the satisfactory endpoint is a dilemma faced by both physicians and patients. Continuing with NUC therapy can reduce the rate of relapse, but unfortunately it can also lead to resistance or virological breakthrough [7].

Available data based on the long-term outcomes following NUC withdrawal in HBeAg-positive CHB patients are insufficient. Hence, we designed this retrospective study, based on 10 years of data on NUC therapy in HBeAg-positive CHB patients, to observe the long-term outcomes of therapy discontinuation once ideal or satisfactory endpoints were achieved.

## Patients and Methods

### Patients

A total of 97 HBeAg-positive CHB patients (86 with HBeAg seroconversion and 11 with HBsAg loss), presenting for treatment at Southwest Hospital from 2002 to 2008, were included in the current study. The patients who started on one antiviral agent, such as lamivudine, and switched to another agent, such as entecavir, because they did not have a good response were classified by the last drug used. Patients were evaluated at least once every 3 months after discontinuation for alanine aminotransferase (ALT), HBV markers and HBV DNA levels. Clinical data were collected, monitored and entered into a database. The outcomes, including sustained response and relapse, were evaluated during long-term follow-up for at least 48 weeks. Data were collected during follow-up appointments through to 1 January 2013.

This analysis was conducted using anonymized data, collected as part of routine patient care. No additional investigations were performed. Therefore, no prior informed consent from the patients was required. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the ethics committee of Southwest Hospital, which waived the need for informed consent.

### Inclusion and exclusion criteria

Criteria for inclusion included: presence of serum HBsAg for at least 6 months; positive for HBeAg; active CHB; and serum HBV DNA levels >20 000 IU/mL, as measured by Lightcycle polymerase chain reaction (PCR) assay (lower limit of detection, 200 IU/mL; Roche Molecular Diagnostics, Basel, Switzerland). An active CHB was defined by a single serum ALT level more than 2.0 times the upper limit of normal (ULN, 40 U/L) or at least two determinations 4 weeks apart of ALT levels 1.0–2.0 $\times$ ULN.

Criteria for exclusion included: coexisting serious medical or psychiatric illness; organ or bone marrow transplantation; recent therapy with systemic corticosteroids, immunosuppressants or chemotherapeutic agents; a serum alpha-fetoprotein level of at least 50 ng/mL; liver disease that was not due to hepatitis B; and seropositivity for human immunodeficiency virus or hepatitis C or D virus.

### Definitions of therapy time and endpoints

The time to achieving HBeAg seroconversion or HBsAg loss was defined as from the commencement of treatment (new agent for switched patients) to the attainment of HBeAg seroconversion or loss of HBsAg. The time on consolidation therapy was defined from the time of achieving HBeAg seroconversion or HBsAg loss to the discontinuation of therapy.

In this study, two endpoints were considered: the ideal and the satisfactory. The ideal endpoint was sustained off-therapy HBsAg loss with or even without anti-HBs seroconversion. The satisfactory endpoint was sustained HBeAg seroconversion and biochemical response for at least 24 weeks.

### Definitions of outcomes after discontinuation

Outcomes after discontinuation were either 'sustained response' or 'virological relapse'. Sustained response was defined as a sustained off-therapy serological, virological and biochemical response. Virological relapse was defined as off-therapy HBV DNA levels >2000 IU/mL in at least two determinations more than 4 weeks apart.

### Serological assays

Routine biochemical tests were performed using automated techniques. HBsAg, antibody to HBsAg, HBeAg, antibody to HBeAg and antibody to hepatitis B core antigen were detected by ELISA (KHB, Shanghai, China) or electrochemiluminescence (Architect®; Abbott Laboratories, Abbott Park, IL, USA). Antibodies to hepatitis C virus, hepatitis D virus and human immunodeficiency virus were detected by routine, commercially available enzyme immunoassays (KHB). Alpha-fetoprotein levels were detected by routine, commercially available colorimetric assay (KHB). The HBV genotypes were determined using an HBV gene type PCR fluorescence kit (Fosun, Shanghai, China).

### Statistical methods

Continuous variables were expressed as mean $\pm$ SD for normal distributions or median and interquartile range (IQR) for abnormal distributions. Pearson's chi-squared tests, Krus-