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When to stop nucleos(t)ide analogues treatment for chronic hepatitis B? Durability of antiviral response

Wonseok Kang, Jun Yong Park

Wonseok Kang, Jun Yong Park, Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul 120-752, South Korea

Wonseok Kang, Jun Yong Park, Liver Cirrhosis Clinical Research Center, Seoul 120-752, South Korea

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Correspondence to: Jun Yong Park, MD, PhD, Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, South Korea. drpjy@yuhs.ac

Telephone: +82-2-22281994 Fax: +82-2-3936884

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Abstract

Introduction of nucleos(t)ide analogues (NAs) for oral antiviral therapy has dramatically improved the clinical outcome in patients with chronic hepatitis B (CHB). Although current international guidelines for the management of CHB provide information regarding when to begin the antiviral therapy with NAs, there is no clear consensus on when to stop the treatment, especially for those who respond to the therapy. Hepatitis B surface antigen loss has been regarded as an ideal endpoint of oral antiviral therapy with NAs, however since this is rarely achieved, practical endpoints have been suggested by the international guidelines. Despite the stopping rules recommended by the international guidelines, whether oral antiviral therapy with NAs can be safely discontinued is of major concern. While attention has been drawn to whether antiviral treatment with NAs can be a finite therapy, there is lack of sufficient

data on off-treatment durability of highly potent NAs. Based on the available evidences, current guidelines for stopping NA therapy seems to be inadequate in terms of off-treatment durability, with relapse rates of more than 40% for both hepatitis Be antigen (HBeAg)-positive and HBeAg-negative patients. Therefore, further studies are required to accumulate data on off-treatment durability of highly potent NAs, and future studies are warranted to identify adequate predictive markers that could provide supplementary information to guide the timing of stopping NA therapy.

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Key words: Chronic hepatitis B; Antiviral therapy; Nucleos(t)ide analogue; Durability; Cessation

Core tip: Introduction of nucleos(t)ide analogues (NAs) for oral antiviral therapy has dramatically improved the clinical outcome in patients with chronic hepatitis B (CHB). While attention has been drawn to whether antiviral treatment with NAs can be a finite therapy in patients with CHB, current guidelines for stopping NA therapy seems to be inadequate in terms of off-treatment durability in both hepatitis Be antigen (HBeAg)-positive and HBeAg-negative patients. In the present work, we discussed the validity of current stopping rules of NA therapy and addressed areas of uncertainty in deciding the best timing to stop NA treatment.

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INTRODUCTION

Hepatitis B virus (HBV) infects more than 350 million

people worldwide and is a major cause of chronic liver disease, which may eventually evolve to cirrhosis and hepatocellular carcinoma (HCC)^[1,2]. There are several host and viral factors which affect the natural course of HBV infection, and active HBV replication has been described as the key driving force for the subsequent HBV-related immune clearance that determine liver injury and progression of liver disease, implicating the importance of sustained viral suppression, or ideally, elimination of the virus^[3].

In recent years, introduction of nucleos(t)ide analogues (NAs) for oral antiviral therapy has dramatically improved the clinical outcome in patients with chronic hepatitis B (CHB). Although current international guidelines for the management of CHB provide information regarding when to begin the antiviral therapy with NAs, there is no clear consensus on when to stop the treatment, especially for those who respond to the therapy.

In this article, we discuss the validity of current stopping rules of NA therapy recommended by the international guidelines by assessing the durability of antiviral response after cessation of NAs based on currently available literature. We also address areas of uncertainty in deciding the best timing to stop NA therapy.

TREATMENT GOALS AND STOPPING RULES

Seroclearance of hepatitis B surface antigen (HBsAg) is a condition that is most similar to complete and definitive remission status of chronic HBV infection. In this view, the international guidelines have suggested HBsAg loss as an ideal endpoint of oral antiviral therapy with NAs. However, HBsAg loss is almost negligible even after a long-term therapy^[4-7]. Therefore it is anticipated that most patients with CHB probably require lifelong oral antiviral treatment with NAs. The primary goals of antiviral therapy are sustained suppression of HBV replication and hepatic inflammation thereby improving long-term outcomes and prolonging patient survival by preventing the development of progressive fibrosis, cirrhosis and/or HCC^[8-10]. Response to treatment is assessed based on biochemical, virological, serological, as well as histological parameters. Treatment with NAs can effectively suppress HBV replication and prevent the progression of disease.

On the other hand, long-term treatment with NAs is associated with significant problems in the management of CHB. Generally, adherence to long-term therapy is an important issue in patient management, and safety of long-term NA treatment is of concern since they are primarily eliminated by the kidney^[11]. Financial burden of long-term NA treatment represent another important issue in the management of CHB. In this regard, international guidelines have suggested the timing of stopping antiviral NAs based on the studies demonstrating off-therapy durability of responses to NA therapy in patients with CHB (Table 1). A finite therapy would not only offer reduced financial burden and increased treatment

Table 1 Criteria for stopping nucleos(t)ide analogue therapy in chronic hepatitis B patients

	HBsAg-positive chronic hepatitis B	HBsAg-negative chronic hepatitis B
APASL 2012	HBeAg seroconversion with undetectable HBV DNA for at least 12 mo	HBsAg seroclearance or NA therapy > 2 yr and undetectable HBV DNA on three separate occasions, 6 mo apart
EASL 2012	HBsAg seroclearance or HBeAg seroconversion with undetectable HBV DNA and 12 mo of consolidation therapy	HBsAg seroclearance
AASLD 2009	HBeAg seroconversion with undetectable HBV DNA and > 6 mo of consolidation therapy	HBsAg seroclearance

HBsAg: Hepatitis Be antigen; APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of Liver; AASLD: American Association of the Study of Liver Disease.

safety but also encourage the patients to stay adherent to the treatment.

For patients with hepatitis B e antigen (HBeAg)-positive CHB, the European Association for the Study of Liver (EASL) guideline recommends HBsAg loss with or without seroconversion as an ideal finite goal of NA therapy^[9]. However, NA therapy-induced HBsAg seroclearance or seroconversion is only achievable in a minority of patients. Hence, the EASL guideline also provides a reasonable option that is comparable to the recommendations of the asian pacific association for the study of the liver (APASL) and american association of the study of liver disease (AASLD) guidelines. The APASL guideline suggests that treatment can be stopped after HBeAg seroconversion with undetectable HBV DNA by a sensitive polymerase chain reaction assay for at least 12 mo^[8]. Likewise, the EASL and AASLD guidelines recommend that treatment can be stopped after HBeAg seroconversion with undetectable HBV DNA and an additional 6-12 mo of consolidation therapy^[9,10].

For patients with HBeAg-negative CHB, however, currently there is no clear consensus on the optimal duration of oral antiviral therapy with NAs. Both the EASL and AASLD guidelines recommend long-term NA therapy until HBsAg seroclearance has been achieved^[9,10]. On the contrary, the APASL guideline suggests that unless HBsAg seroclearance has been achieved, cessation of NA therapy can be considered after at least 2 years of treatment if HBV DNA remains undetectable on three separate occasions 6 mo apart^[8].

Despite the stopping rules recommended by the international guidelines, whether oral antiviral therapy with NAs can be safely discontinued is of major concern. Accordingly, many studies have been conducted to evaluate the durability of antiviral response after cessation of NAs in patients with CHB (Table 2).

Table 2 Off-therapy durability of response to nucleos(t)ide analogue therapy in chronic hepatitis B patients

Ref.	NA	n	Treatment duration	Cumulative relapse rate
HBeAg-positive CHB				
Song <i>et al</i> ^[13]	LMV	98	10.3 ± 3.1 mo	1 yr, 37.5%; 2 yr 49.2%
Chien <i>et al</i> ^[14]	LMV	82	16 (3-55) mo	48% ¹
Dienstag <i>et al</i> ^[12]	LMV	39	36.6 (4.8-45.6) mo	77% ¹
Ryu <i>et al</i> ^[18]	LMV	61		6 mo, 15%; 1 yr, 21%; 2 yr, 31%
van Nunen <i>et al</i> ^[15]	LMV	59		3 yr, 54%
Byun <i>et al</i> ^[16]	LMV	132	14 ± 7 mo	6 mo, 58%; 1 yr, 66%
Yoon <i>et al</i> ^[17]	LMV	95	26 mo	1 yr, 52%; 2 yr, 55.7%
Fung <i>et al</i> ^[44]	LMV	22	23 (5-91) mo	44% ¹
Lee <i>et al</i> ^[19]	LMV	178	26 (12-77) mo	1 yr, 15.9%; 5 yr, 30.2%
Reijnders <i>et al</i> ^[21]	Various	132	26 (16-43) mo	67% ¹
Wang <i>et al</i> ^[20]	LMV	82	24 (12-54) mo	1 yr, 23.4%; 2 yr, 25.0%; 4 yr, 29.4%
Chaung <i>et al</i> ^[22]	Various	39		90% ¹
HBeAg-negative CHB				
Santantonio <i>et al</i> ^[23]	LMV	15	52 wk	74% ¹
Fung <i>et al</i> ^[24]	LMV	50	2 yr	6 mo, 30%; 12 mo, 50%; 18 mo, 50%
Chien <i>et al</i> ^[45]	LMV	85	7.4 (6-12) mo	61% ¹
Chan <i>et al</i> ^[46]	LMV	139	24 mo	90% ¹
Shouval <i>et al</i> ^[47]	ETV	257	48 wk	3% ¹
	LMV	201	48 wk	5% ¹
Paik <i>et al</i> ^[25]	LMV	50	24 mo	1 yr, 20.9%; 2 yr, 36.0%; 3 yr, 43.1%
Liu <i>et al</i> ^[26]	LMV	61	≥ 24 mo	6 mo, 26.2%; 1 yr, 43.6%; 5 yr, 56.1%
Hadziyannis <i>et al</i> ^[27]	ADV	33	≥ 4 yr	45% ¹
Jeng <i>et al</i> ^[28]	ETV	95	721 (395-1762) d	1 yr, 45.3%
Kim <i>et al</i> ^[48]	Various	45		6 mo, 48.9%; 1 yr, 73.3%

¹Overall relapse. NA: Nucleos(t)ide analogue; CHB: Chronic hepatitis B; LMV: Lamivudine; ETV: Entecavir; ADV: Adefovir dipivoxil.

OFF-THERAPY DURABILITY OF ANTIVIRAL RESPONSE

HBeAg-positive patients

Initial studies with lamivudine showed disappointing results with its antiviral durability after cessation of therapy. Although a study of 39 patients reported lamivudine-induced HBeAg seroconversion to be durable in 77% of patients^[12], a subsequent study of 34 HBeAg-positive CHB patients in whom lamivudine was stopped after HBeAg seroconversion showed that the cumulative relapse rate was 37.5% after 1 year and increased to 49.2% after 2 years of discontinuation^[13]. Similarly, Chien *et al*^[14] also reported that 48% of the patients relapsed after discontinuing lamivudine for 12 mo. In parallel with these results, several studies from different groups showed that the off-treatment durability of lamivudine-induced HBeAg seroconversion was not sustained in a large proportion of patients, with cumulative relapse rate of more than 50% after 1 year^[15-17].

On the other hand, some studies have reported a higher antiviral durability after cessation of therapy. In a study of 61 patients, Ryu *et al*^[18] reported that the cumulative relapse rate was 15% at 6 mo and 31% at 2 years after stopping lamivudine therapy. A more recent study by Lee *et al*^[19] also showed a durable off-treatment response in 178 patients with lamivudine-induced complete response. In this study, the cumulative relapse rate was 15.9% at 1 year and 30.2% at 5 years. These results were supported by a more recent prospective study with 82 patients demonstrating a cumulative relapse rate of

23.4% at 6 mo and 29.4% at 4 years after discontinuation of lamivudine^[20].

However, in a series of recent studies with various antiviral NAs the off-treatment response was shown to be not durable despite consolidation therapy after HBeAg seroconversion. A study of 132 patients who achieved HBeAg seroconversion by various NAs demonstrated an overall relapse rate of 67% despite consolidation therapy after HBeAg seroconversion^[21]. Moreover, a more recent study of 39 patients treated with various NAs reported that almost all (90%) patients who stopped NA therapy after achieving HBeAg seroconversion and clinical response experienced recurrent viremia despite consolidation therapy prior to discontinuation of NAs^[22].

To summarize, the results from these studies imply that the current guidelines of stopping NAs after achieving HBeAg seroconversion with undetectable HBV DNA do not seem to result in a durable off-treatment antiviral response in the majority of HBeAg-positive CHB patients.

HBeAg-negative patients

Earlier studies showed consistent results that the antiviral response was not durable in patients who stopped NA therapy even if the guideline recommendations were followed. In a small study of 15 HBeAg-negative patients who stopped lamivudine after a year of therapy, 86% of the patients developed virological and/or biochemical relapse^[23]. Succeeding studies with more stringent cessation criteria showed some improvements in the durability of NA-induced antiviral response, yet the results were

still disappointing. In a retrospective study of 50 HBeAg-negative patients, the cumulative relapse rates at 6 mo was 30% and at 18 mo was 50% despite successful lamivudine treatment for 2 years followed by withdrawal^[24]. Moreover, several prospective studies also demonstrated that off-treatment response rates were below satisfaction. In a long-term prospective study of 50 HBeAg-negative patients who stopped lamivudine after treatment for 24 mo, the cumulative relapse rate was 43.1% at 3 years after withdrawal^[25]. Similarly, Liu *et al*^[26] have also reported a cumulative relapse rate of 56.1% at 5 years after stopping lamivudine treatment.

In a series of recent studies with antiviral NAs other than lamivudine, the durability of off-treatment response was shown to be comparable to that of lamivudine treatment. A prospective cohort study of 33 HBeAg-negative patients who had been treated with adefovir for 4-5 years and monitored for 5.5 years after cessation of treatment showed an overall relapse rate of 45% during the follow-up period^[27]. Interestingly, among 18 of 33 patients who achieved sustained response, 13 (72%) patients showed HBsAg clearance. Of note, serum HBsAg levels at the end of treatment showed significant association with HBsAg clearance, suggesting a possible role of HBsAg quantitation for predicting the antiviral response to NA therapy.

A more recent study by Jeng *et al*^[28] demonstrated off-treatment durability of entecavir therapy in 95 HBeAg-negative patients using the stopping rule recommended by the APASL guideline. In this observational study, patients were treated with entecavir for a median of 721 d, and followed up for at least 12 mo. The cumulative relapse rate after 1 year of stopping entecavir treatment was 45.3%.

For the patients with HBeAg-negative CHB, current data show that about half of the patients attain durable antiviral response after discontinuation of NA therapy. This is somewhat disappointing as the off-treatment durability is not satisfactory despite following the stopping rule recommended by the guideline. Therefore, further studies would be required to find adequate factors that could predict the best timing of stopping the NA therapy.

HBSAG QUANTITATION AS A PREDICTIVE MARKER

Current guidelines for stopping NA therapy seems to be inadequate in terms of off-treatment durability, with relapse rates of more than 40% for both HBeAg-positive and HBeAg-negative patients. As a result, further studies are warranted to identify adequate predictive markers that could provide supplementary information to guide the timing of stopping NA therapy.

One of the recently proposed predictive factors for HBsAg loss is serum HBsAg quantitation. Since serum HBsAg level seems to correlate with the amount of covalently closed circular DNA (cccDNA) within the infected hepatocytes^[29-31], serial monitoring of serum HBsAg

levels during the course of antiviral therapy may provide useful information regarding off-treatment response. Clinically, low serum levels of HBsAg and HBV DNA were reported to be predictive of spontaneous HBsAg seroclearance in treatment-naïve patients^[32]. For HBeAg-positive patients on NA therapy, older age, high baseline alanine aminotransferase and HBeAg loss were reported as the predictive factors for HBsAg loss^[33]. Based on these findings, it has been suggested that monitoring of serum HBsAg levels along with serum HBV DNA levels may guide the timing of stopping NA therapy^[34]. However, the clinical significance of serum HBsAg quantitation for predicting HBsAg loss during antiviral therapy with NAs has been challenged by several studies. In a study investigating the effect of long-term entecavir or tenofovir treatment on serum HBsAg levels in CHB patients, Zoutendijk *et al*^[35] reported that the predicted median time to HBsAg loss was 36 years for HBeAg-positive and 39 years for HBeAg-negative patients. Moreover, another study from a French group, based on their mathematical modeling, suggested that more than 50 years of NA therapy would be required for the clearance of HBsAg^[35], implying that cessation of NA therapy would be almost impossible. Nevertheless, there is an increasing attention in the clinical utility of serum HBsAg quantitation, and further studies are needed to validate its role for monitoring the antiviral response and predicting the off-treatment durability.

CONCLUSION

For the minority who have achieved the ultimate goal of NA therapy, *i.e.*, HBsAg loss, the treatment may be discontinued. However, loss of HBsAg does not necessarily indicate complete eradication of the virus as cccDNA persists within the infected hepatocytes, and thus there is still a risk of developing HCC^[36,37]. Therefore, long-term surveillance for HCC would be mandatory albeit successful achievement of HBsAg loss and discontinuation of NA therapy.

In addition, for patients with liver cirrhosis, it would be beneficial to maintain than to discontinue NA therapy. This is supported by an increasing data that long-term viral suppression with NA therapy not only decreases hepatic inflammation but also induces regression of cirrhosis which may translate to improved clinical outcome^[38-43].

In conclusion, while attention has been drawn to whether antiviral treatment with NAs can be a finite therapy, there is lack of sufficient data on off-treatment durability of highly potent NAs, particularly tenofovir, and based on the available evidences, current guidelines for stopping NA therapy seems to be inadequate in terms of off-treatment durability. Therefore, further studies are required to accumulate data on off-treatment durability of highly potent NAs. Furthermore, search for adequate predictive markers that could provide supplementary information to guide the timing of stopping NA therapy is warranted. Clinical studies addressing this issue seems to be highly desirable in the future.

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