

Cases From the Field

Sustained Off-Treatment Response After Discontinuation of Long-Term Nucleos(t)ide Analogue Treatment in HBeAg-Seronegative Hepatitis B: A Case Series

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International guidelines recommend lifelong nucleos(t)ide analogue (NA) treatment in individuals with chronic hepatitis B (CHB) infection who are hepatitis B e antigen (HBeAg) seronegative, because hepatitis B surface antigen (HBsAg) seroconversion is rarely achieved. However, after terminating therapy, sustained responses and HBsAg loss have been observed. Clinical characteristics identifying persons with favorable outcomes after discontinuing NA therapy have not yet been defined. This case series describes outcomes of 6 individuals with HBeAg-seronegative CHB infection without cirrhosis and low plasma levels of HBsAg who discontinued long-term NA treatment. All individuals had a virologic relapse and 4 of 6 had a biochemical relapse; but 5 of 6 later developed a sustained virologic and biochemical response and a marked reduction of quantitative HBsAg (qHBsAg). Two of the 6 individuals experienced HBsAg loss. Only 1 patient was retreated, and none showed signs of hepatic decompensation. NA treatment can be safely stopped in selected HBeAg-seronegative patients. Sustained off-treatment responses seem to be frequently preceded by a virologic and biochemical flare. Loss of HBsAg possibly reflects restoration of antiviral immunity during prolonged NA treatment. Predictive factors, such as qHBsAg, may be valuable in selecting patients who could benefit from NA discontinuation.

Keywords: Hepatitis, chronic, hepatitis B, HBeAg, CHB, nucleos(t)ide analogue, treatment

Introduction

The duration of nucleos(t)ide analogue (NA) therapy is an unresolved issue in the treatment of persons with chronic hepatitis B (CHB) infection who are hepatitis B e antigen (HBeAg) seronegative. In these individuals, HBeAg clearance or seroconversion to hepatitis B e antigen antibodies (anti-HBe) cannot be used as an endpoint, and the treatment goal

of hepatitis B surface antigen (HBsAg) clearance or HBsAg antibody (anti-HBs) seroconversion is rarely achieved.¹ American and European CHB infection guidelines recommend lifelong NA therapy for patients with CHB infection who are HBeAg seronegative.^{2,3} These recommendations are unsatisfactory for several reasons. First, although NA therapy is well tolerated in general, the issue of potential long-term adverse effects is still unresolved. Second, the cost of lifelong therapy represents a considerable financial burden and may not be affordable in countries with limited financial resources. Finally, the prospect of strict adherence to lifelong therapy can inflict a substantial psychological strain on the individual.

Defining rules for stopping NA therapy in individuals with CHB infection who are HBeAg seronegative is important. However, factors that can predict a favorable off-treatment response are presently unknown as is the typical clinical course after NA discontinuation. This case series presents the biochemical, serologic, and virologic responses of 6 carefully selected HBeAg-seronegative patients with CHB infection who discontinued long-term NA therapy.

Case Descriptions

Individuals with CHB infection who were HBeAg seronegative and presented at our outpatient clinic between September 2011 and January 2014 had to meet specific criteria for discontinuing NA treatment. These criteria included hepatitis B virus (HBV) mono-infection; treatment duration of more than 5 years with a complete virologic and biochemical response; quantitative HbsAg (qHBsAg) level below 2000 IU/mL; no signs of advanced liver disease on liver function test results; and an absence of more than mild fibrosis as shown in abdominal ultrasound and elastography.

This is not a prospective study with documented informed consent but a retrospective review of persons who stopped therapy. The patients did receive detailed information about potential risks associated with treatment discontinuation, including hepatitis flare and liver failure. After careful

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Table 1. Characteristics of Patients With HBe Antigen–Seronegative Chronic Hepatitis B Infection at End of Treatment

Patient #	Age (years), Sex	Previous NA Therapy	Duration of Therapy (years)	Viral Load <LOD (years)	Genotype	qHBsAg (IU/mL)
1	62, female	Lamivudine	12	11	Unknown	730
2	55, female	Lamivudine, adefovir, tenofovir disoproxil fumarate, entecavir	12	8	B	790
3	61, male	Lamivudine, adefovir, tenofovir disoproxil fumarate	13	4	Unknown	0 ^a
4	45, male	Lamivudine, adefovir, tenofovir disoproxil fumarate	9	4	D	1900
5	36, male	Entecavir, tenofovir disoproxil fumarate	6	6	E	123
6	56, male	Lamivudine, adefovir, tenofovir disoproxil fumarate	11	6	D	620

Abbreviations: LOD, limit of detection; NA, nucleos(t)ide analogue; qHBsAg, quantitative hepatitis B surface antigen.

^aQuantitative HBsAg became negative in this person during NA treatment.

consideration, 6 persons were approved to discontinue NA therapy. After treatment cessation, the individuals were monitored clinically, biochemically (liver enzyme levels), and virologically (HBV DNA level) every 4 weeks for the first 3 months and every 3 months thereafter. Virologic relapse was defined as HBV DNA levels of 2000 IU/mL or more and biochemical relapse as an alanine aminotransferase (ALT) level above the upper limit of normal (ULN). Conversely, virologic and biochemical responses were defined by an HBV DNA level of 2000 IU/mL or less and an ALT level below ULN, respectively.

Patient characteristics before the end of treatment (EOT) are presented in Table 1. The median age at EOT was 55.5

years. One person was Asian, 1 person was African, and the others were white. The median duration of NA therapy was 11.5 years; the median duration of suppressed viral load was 7 years. Outcomes after treatment cessation are summarized in Table 2. All patients showed a virologic relapse, and 4 of 6 showed a biochemical relapse with peak values 2 months after EOT. In one individual (patient 4), the ALT level continued to be elevated and the HBV DNA level remained high (> 2000 IU/mL). This person was asymptomatic and did not show signs of impaired liver function (ie, normal bilirubin level and international normalized ratio) at all times. Upon resuming therapy at week 24, this patient reached viral suppression after another 12 weeks. All other persons remained off treatment and showed a sustained virologic and biochemical response. In individuals with a

sustained virologic response, HBV DNA level dropped below 2000 IU/mL until month 3 and ALT levels normalized until month 4 after EOT. Except for 1 individual who was retreated (patient 4) and 1 individual who was qHBs seronegative at EOT (patient 3), qHBs decreased or became negative in all patients. In 2 persons, complete loss of HBsAg and hepatitis B surface antibodies (anti-HBs) occurred.

Discussion

In this case series, favorable outcomes after discontinuing long-term NA treatment were observed in HBeAg-

Table 2. Off-Treatment Responses of Patients With Hepatitis B e Antigen–Seronegative Chronic Hepatitis B Infection After Treatment Discontinuation

Patient #	Relapse		Off-Treatment Response				
	Peak VL (IU/mL) /month	Peak ALT (ULN) /month	Month with VL <2000 IU/mL	Month with ALT <ULN	Minimal qHBsAg (IU/mL)/month	Anti-HBs (IU/mL) /month	Follow-up (months after EOT)
1	6030/2	2x/2	3	3	274/36	None	36
2	34,200/2	None	3	0	1.76/50	None	45
3	9890/2	1.5x/2	3	3	0/0	>1000/6	40
4	495,000,000/2	10x/2	Patient was retreated; viral suppression was achieved at month 6 after reinitiation of tenofovir disoproxil fumarate				48
5	8110/2	None	3	0	0/15	12/23	23
6	2,060,000/2	49x/2	3	4	0/8	None	16

Abbreviations: ALT, alanine aminotransferase; anti-HBs, hepatitis B surface antibodies; EOT, end of treatment; qHBsAg, quantitative hepatitis B surface antigen; ULN, upper limit of normal; VL, viral load.

seronegative persons with CHB infection who did not have cirrhosis. Five of 6 persons had sustained off-treatment biochemical and virologic response, 2 of 6 persons lost HBsAg, and 2 of 6 persons developed anti-HBs seroconversion. A hepatic flare after treatment discontinuation occurred in 4 individuals but did not lead to hepatic decompensation. These results add to the growing evidence that NA treatment cessation not only is safe in individuals without cirrhosis and poses a promising therapeutic option for selected individuals with CHB infection who are HBeAg seronegative. Presently, the question of treatment duration in individuals with CHB infection who are HBeAg seronegative is a matter of debate. Although European and US guidelines recommend NA treatment cessation 12 months after anti-HBe seroconversion for HBeAg-seropositive patients,^{2,3} there is no generally accepted stopping rule for those who are HBeAg seronegative. Most studies reporting about treatment discontinuation in HBeAg-seronegative individuals focused on cumulative relapse rates rather than on analysis of sustained off-treatment responses.⁴ Further, the methods and analyses of these studies vary with respect to NA treatment duration, viral suppression duration, application of discontinuation rules, definition of outcomes, and length of follow-up. For these reasons, the therapeutic value of NA treatment cessation in individuals with CHB infection who are HBeAg seronegative is unclear as are the factors in identifying those most likely to have a favorable outcome.

Toward that end, a pilot study by Hadzyannis and colleagues showed promise.⁵ In the study, 33 HBeAg-seronegative patients with CHB infection in whom complete viral suppression was achieved with adefovir had their treatment discontinued after 4 to 5 years of continuous therapy. These persons all experienced a virologic relapse, and 76% experienced a biochemical relapse soon after treatment ceased. However, 55% of these persons subsequently had a virologic and biochemical response, and 39% experienced HBsAg loss. Based on data suggesting that prolonged viral suppression allows for a substantial restoration of antiviral T-cell immunity,⁶ the biochemical relapse after NA discontinuation was interpreted as a hepatitis flare caused by restored antiviral immunity.

The observations presented in our case series are in agreement with the concept proposed by Hadzyannis. Although all 6 individuals in our series had a virologic relapse and 4 of 6 persons (67%) had a biochemical relapse during the first 2 months after treatment discontinuation, 5 of 6 individuals (83%) later developed a sustained virologic and biochemical response. In addition, in these individuals with a sustained response, qHBsAg levels decreased markedly, and in 2 individuals anti-HBs seroconversion occurred. In total, 5 of 6 persons (83%) experienced persistent loss of or a strong reduction in HBsAg after discontinuing NA treatment. In comparison, during the first 4 to 5 years of NA treatment, HBsAg loss is virtually never observed,¹ and the rate of annual HBsAg loss under continual NA treatment has been reported to be as low as 0.33%.⁷ Because loss of HBsAg in HBeAg-seronegative individuals with CHB infection is regarded as

the closest equivalent to a clinical cure, the excellent overall outcomes demonstrated by persons in this case series emphasize the strong potential of NA treatment discontinuation in selected individuals.

In order to formalize this concept into a clinical rule for treatment discontinuation, valid predictive factors for identifying patients who could safely and successfully stop treatment need to be defined. Because these factors have not yet been identified, criteria for when patients could safely stop treatment in this retrospective review were based on evidence about safety and sustained off-treatment responses described in earlier studies. As summarized recently, in 22 studies with a total of 1732 patients, only 1 episode of hepatic decompensation in a patient with liver cirrhosis was reported.⁸ Therefore, treatment discontinuation was offered only to CHB patients who did not show signs of cirrhosis or advanced liver fibrosis as indicated by biochemical test results and abdominal ultrasound and elastography. Furthermore, all 6 individuals in the series had received long-lasting suppressive NA therapy (>6 years) before treatment was discontinued.⁵ In the absence of adequate study data, the duration of NA treatment necessary to restore antiviral immune function is presently unknown. However, treatment duration does seem to play a role, as earlier studies showed relapse rates as high as 90% after 1 year of NA treatment,⁹ whereas subsequent studies with longer treatment periods reported far better sustained response rates.¹⁰⁻¹² Finally, treatment was discontinued in individuals with low levels of HBsAg (<2000 IU/mL), because low qHBsAg level at EOT was associated with sustained biochemical response in retrospective studies in Asian patients¹³⁻¹⁵ and with HBsAg loss in a multivariate analysis of the Hadzyannis study.⁵

In summary, the results of this case series suggest that treatment cessation in individuals with CHB infection who are HBeAg seronegative and do not have cirrhosis is safe and, as reflected by a high rate of HBsAg loss and anti-HBs seroconversion, may prove to be a therapeutic option for some patients. However, stringent patient selection is likely crucial, and the criteria for selecting patients who could benefit from NA discontinuation will have to be defined in properly designed prospective studies. 

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Correction note: An earlier version of this article listed the wrong nucleos(t)ide analogue therapy in Table 1. It should be entecavir, not etravarinine as originally stated.