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ORIGINAL RESEARCH

Hepatitis B surface antigen seroclearance after nucleos(t)ide analogue discontinuation in non-cirrhotic patients with chronic hepatitis B

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Highlights & Insights

- **Scientific Gap:** HBsAg seroclearance occurred in 11.0% of patients after nucleos(t)ide analogue discontinuation, whereas no seroclearance was observed during continued treatment.
- **Key Finding:** Clinical relapse occurred in 39.7% of patients after treatment discontinuation, with 72% of relapses occurring within the first 3 months.
- None of the patients who achieved HBsAg seroclearance experienced clinical relapse, and 75% developed anti-HBs.
- **Clinical Impact:** Nucleos(t)ide analogue discontinuation may increase the likelihood of functional cure in carefully selected non-cirrhotic, HBeAg-negative patients, provided that close post-treatment monitoring is ensured.

ABSTRACT

Background and Aim: This study aimed to evaluate the clinical outcomes following the discontinuation of nucleos(t)ide analogue (NA) treatment in hepatitis B e antigen (HBeAg)-negative patients with chronic hepatitis B (CHB).

Materials and Methods: This single-center retrospective cohort study included 146 non-cirrhotic patients with CHB who achieved long-term viral suppression under NA treatment. Seventy-three patients discontinued NA treatment, while a historical age- and sex-matched control group consisted of 73 patients who continued NA treatment.

Results: Hepatitis B surface antigen (HBsAg) seroclearance occurred in eight patients (11%) in the treatment-discontinuation group, while none was observed in the treatment-continued group ($p = 0.004$). The cumulative probability of HBsAg loss was 16.9% at month 120 after NA discontinuation. Firth-penalized Cox regression analysis identified younger age (<50 years) at treatment discontinuation ($p=0.023$) and elevated baseline serum AST levels ($p=0.018$) as independent predictors of HBsAg seroclearance. Seventy-five percent of these patients experienced HBsAg seroconversion to hepatitis B surface antibody (anti-HBs). After NA discontinuation, 67% of the patients (49/73) in the treatment-discontinuation group experienced virological relapse. Of these, 29 developed clinical relapse and reinitiated antiviral treatment, while the remaining 20 patients continued follow-up without antiviral therapy. Most clinical relapses (72%) occurred within the first 3 months after treatment discontinuation. Virological relapse did not occur in the other 24 patients. Overall, 44 patients in the treatment-discontinuation group (60%) did not require retreatment during follow-up.

Conclusion: Discontinuation of long-term NA treatment in selected HBeAg-negative patients was associated with HBsAg seroclearance and may contribute to a functional cure. Close post-discontinuation surveillance remains essential for early detection and management of clinical relapse.

Keywords: Antiviral therapy discontinuation, HBsAg Seroclearance, Hepatitis B virus.

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Introduction

Chronic hepatitis B virus (HBV) infection continues to pose a significant public health concern globally, affecting approximately 250 million individuals.[1,2] HBV accounts for most adult cases of cirrhosis and hepatocellular carcinoma (HCC) in Türkiye.[3–5] A 2009 epidemiological study found that the prevalence of hepatitis B surface antigen (HBsAg) was approximately 4%, with more than 2 million adults testing positive for HBsAg in Türkiye.[6]

Nucleos(t)ide analog (NA) antiviral therapy provides effective long-term viral suppression and mitigates disease progression in patients with chronic hepatitis B (CHB). The primary goal of antiviral treatment for HBV is to eliminate HBsAg and achieve seroconversion to hepatitis B surface antibody (anti-HBs). Unfortunately, HBsAg seroclearance rarely occurs after long-term NA treatment with current antiviral therapies.[2,7] HBsAg loss was observed in approximately 10% of patients with hepatitis B e antigen (HBeAg)-positive and around 1% of HBeAg-negative patients after 8 years of tenofovir disoproxil fumarate (TDF) treatment.[8,9] Consequently, many patients with HBeAg-negative require indefinite therapy, which presents challenges related to adherence, cumulative drug exposure, and potentially side effects, antiviral resistance, and long-term healthcare costs.[2,7,10] Emerging evidence from randomized trials and real-world studies has reignited interest in discontinuing NA therapy to stimulate host immune responses that may lead to HBsAg seroclearance.[11–13]

According to previous studies, NA treatment may be discontinued in selected patients with CHB.[7,12–14] In some cases, discontinuation of NA treatment can lead to a functional cure by triggering immune control.[12–16] However, the data are heterogeneous and scarce. Additionally, previous studies do not clearly define the characteristics of the selected patients. In this single-center study, we examined the clinical outcomes of NA discontinuation in a rigorously selected cohort of non-cirrhotic, HBeAg-negative patients with CHB.

Materials and Methods

Study Design and Patient Population

This is a retrospective, single-center observational cohort study conducted at the Liver Diseases Outpatient Clinic. Chronic HBV infection was diagnosed and treated based on the European Association for the Study of the Liver guideline.[7] A total of 852 patients with CHB who were followed at our center between January 2014 and December 2024 were screened for eligibility. The study protocol was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (approval number: 2025/393, date: 22/05/2025) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Patient Selection, Study Groups, and Monitoring Protocol

All patients in the screened cohort were evaluated using the same eligibility and exclusion criteria before being classified by treatment status. Eligible patients were adults with non-cirrhotic, HBeAg-negative CHB who had received licensed oral NA for at least 5 years, maintained virological suppression, defined as undetectable serum HBV DNA, for at least 3 years before the index date, and had normal serum ALT levels. Patients with cirrhosis, a history of hepatic decompensation, liver stiffness greater than 10 kPa, hepatocellular carcinoma, viral coinfection, another concomitant liver disease, or insufficient clinical follow-up were excluded. The discontinuation of NA treatment was conducted in accordance with local regulations. Of the 477 eligible patients, 73 had discontinued NA treatment, and 404 had continued treatment. Propensity scores based on age and sex were used for 1:1 matching without replacement. Each patient in the discontinuation group was matched to one patient in the continuation group with a maximum absolute propensity score difference of 0.01. The final matched cohort included 146 patients: 73 in the NA-discontinuation group and 73 in the NA-continuation group. The index date was defined as the NA discontinuation date for the discontinuation group and the corresponding cohort-entry date for the matched continuation group. The patient-selection process is presented in Figure 1.

Laboratory Measurements

Laboratory parameters, including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), bilirubin, and complete blood cell counts, were measured at baseline and during follow-up using standard automated methods in our institution's central laboratory. Baseline laboratory values were those obtained immediately before initiation of NA treatment. Histological activity and fibrosis stage were based on the pretreatment liver biopsy. Quantitative HBsAg at NA discontinuation was measured using the Elecsys HBsAg II Quant assay (Roche Diagnostics, Mannheim, Germany). Serum HBV DNA levels were assessed using the Cobas TaqMan assay (Roche Diagnostics, Branchburg, NJ, USA) with a lower limit of detection of 20 IU/mL.

Definitions and Study Endpoints

The primary endpoints of the study were to investigate sustained HBsAg seroclearance and to identify factors associated with seroclearance. HBsAg seroclearance was defined as the loss of detectable HBsAg for at least six months, with or without seroconversion to anti-HBs following discontinuation of NA treatment. The secondary endpoints included virological, biochemical, and clinical relapse through the last follow-up. Virological relapse was defined as a serum HBV DNA level >2,000 IU/mL at any time after NA discontinuation, whereas biochemical relapse was defined as an increase in serum ALT to >2× the upper limit of normal. Clinical relapse was defined as the concomitant occurrence of virological and biochemical relapse. TDF, entecavir (ETV), or tenofovir alafenamide (TAF) was immediately recommended at the physician's discretion in cases of clinical relapse.

Follow-up

Patients were regularly seen in an outpatient clinic. Laboratory tests were performed during this period. Serum ALT and HBV DNA levels

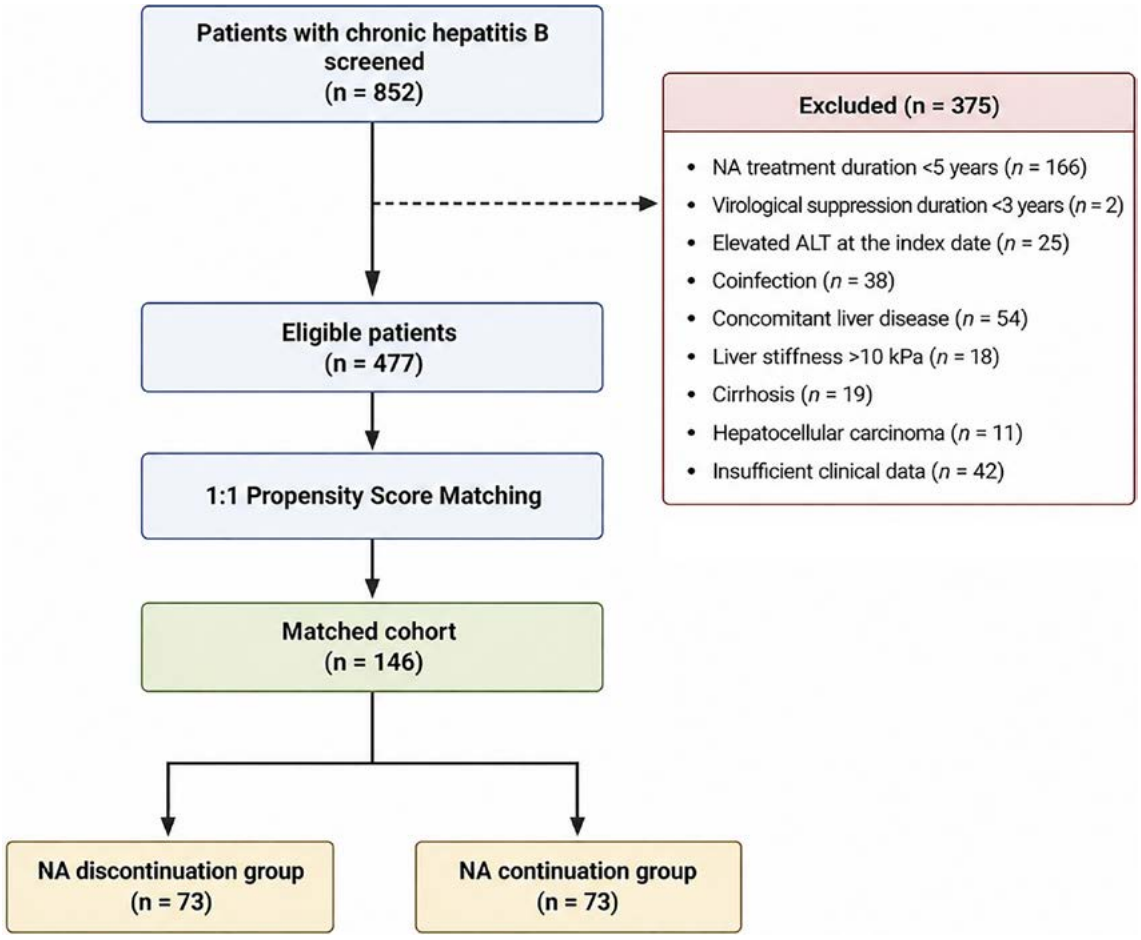


Figure 1. Flowchart illustrating patient selection and propensity score matching.

were serially monitored on the 3rd, 7th, 14th, 28th, 56th days in the discontinuation group, and every three months in both groups.

Statistical Analysis

To minimize confounding factors introduced by the retrospective, and nonrandomized design, 1:1 propensity score matching was performed by age and gender. The propensity score without replacement was calculated with a binary logistic regression for each patient. For the matching process, the tolerance for the score in matching cases and controls was set at 0.01. A control is eligible to match a case if the absolute value of the difference in the propensity scores is less than or equal to 0.01. Descriptive statistics are summarized as counts and percentages for categorical variables, mean and standard deviations for normally distributed continuous variables, and median and interquartile range for ordinal and non-normally distributed continuous variables. The differences in proportions between groups were compared using the Chi-Square, Fisher's Exact tests or Fisher-Freeman-Halton Exact Test, where appropriate. The Mann-Whitney U test was used to compare two groups regarding ordinal or non-normally distributed continuous variables. The survival estimations were performed using the Kaplan-Meier algorithm, and the comparison between groups was evaluated with the Log-rank test. Variables with a p-value <0.25 in the univariable Firth penalized Cox proportional hazards regression were considered candidates for the multivariable Firth penalized Cox model. Variables of established clinical importance were also included, irrespective of their univariable significance, using a purposeful selection approach. The final model was constructed using variables with a p-value less than 0.05, which were considered statistically significant. The hazard ratio (HR) and the associated 95% confidence interval (CI) were calculated. Statistical analyses were performed using IBM SPSS Statistics version 30.0 (IBM Corp., Armonk, NY, USA). A two-tailed P-value less than 0.05 was considered statistically significant.

Results

A total of 146 non-cirrhotic patients with HBeAg-negative CHB were included in the analysis: 73 patients in the NA discontinuation group and 73 in the NA continuation group. The median age of the patients was 52.5 years, and the majority of patients were male (56%). There were no significant differences in baseline characteristics among patients, except that the histological activity index (HAI) was higher in the NA discontinuation group (p<0.001), (Table 1). The median duration of NA therapy before discontinuation was 93 months (IQR: 72–120). The median follow-up duration after NA discontinuation was 44 months (IQR: 25-89).

Table 1. Characteristics of the matched study cohort

Characteristic	Overall (n=146)	NA discontinuation (n=73)	NA continuation (n=73)	p
Age at the index date (years)	52.5 (44–59)	53 (44–59)	52 (45–59)	0.943
Sex, male/female (%)	56/44	56/44	56/44	1.000
Disease duration at the index date (months)	205.0 (160–229)	205.0 (176–225)	205.0 (138–232)	0.707
Serum HBV DNA (log10 IU/mL)	5.38 (4.28–6.74)	5.37 (4.0–6.7)	5.38 (4.7–6.8)	0.405
Serum ALT (U/L)	56 (24–113)	48 (23–117)	57.5 (27–112)	0.592
Serum AST (U/L)	35 (23–62)	33 (22–81)	35 (25–53)	0.948
Serum GGT (U/L)	23 (16–35)	22 (15–35)	24 (16–34)	0.576
Total bilirubin (mg/dL)	0.75 (0.53–1.0)	0.7 (0.5–1.1)	0.8 (0.6–1.0)	0.892
Albumin (g/dL)	4.3 (4.1–4.5)	4.3 (4.1–4.5)	4.3 (4.1–4.5)	0.821
Platelet count ($\times10^3$/μL)	220 (183–269)	218 (184–277)	221 (183–264)	0.601
INR	1.0 (0.96–1.0)	1.0 (0.97–1.0)	1.0 (1.0–1.1)	0.506
HAI on liver biopsy	7 (5.5–9.0)	8 (6.0–9.0)	6.0 (5–8)	<0.001
Fibrosis score	1 (1–2)	1 (1–2)	2 (1–2)	0.122
NA treatment at the index date, n	27 ETV 105 TDF 14 other	12 ETV 50 TDF 11 other	15 ETV 55 TDF 3 other	0.0764

Data are presented as median (25^{th}–75^{th} percentiles), percentage, or count, as appropriate. Laboratory and histological variables are pretreatment values obtained before NA initiation; age and disease duration were assessed at the index date. The index date was the date of NA discontinuation for the discontinuation group and the matched cohort-entry date for the continuation group. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CHB: Chronic hepatitis B; ETV: Entecavir; GGT: Gamma-glutamyl transferase; HAI: Histological activity index; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; INR: International normalized ratio; NA: Nucleos(t)ide analogue; TDF: Tenofovir disoproxil fumarate. Other NAs included lamivudine and telbivudine.

HBsAg seroclearance was observed in eight patients in the NA discontinuation group, compared to none in the treatment continuation group (p=0.004). HBsAg seroclearance occurred progressively over time. The cumulative probability of HBsAg seroclearance, estimated using the Kaplan–Meier method, reached 16.9% at 120 months (Fig. 2). The median time to HBsAg seroclearance after NA discontinuation was 4.5 months (range, 1 to 81 months). There were no significant differences in baseline characteristics between patients with and without HBsAg seroclearance (Table 2). Firth-penalized Cox regression analysis revealed that only younger age (<50 years) at treatment discontinuation (hazard ratio [HR], 5.72; 95% confidence interval [CI], 1.26–35.01; p=0.023) and elevated baseline AST levels (HR, 6.29; 95% CI, 1.36–39.96; p=0.018) were independently associated with HBsAg seroclearance in patients with CHB (Table 3). Six (75%) patients experienced HBsAg seroconversion to anti-HBs.

After NA discontinuation, 67% of patients (49/73) in the treatment-discontinuation group experienced virological relapse. Virological relapse was first detected in 19 patients during the first month, 15 during the second month, 5 during the third month, 2 during the fourth month, 4 during the fifth month, and 4 during the sixth month. Virological relapse did not occur in the remaining 24 patients. Of these patients with virological relapse, 29 developed clinical relapses. Most clinical relapses (72%) occurred within the first 3 months after treatment discontinuation. The median time from NA discontinuation to relapse was 2 months (range, 1–60 months). Of these patients, nine had ALT levels >3×ULN, seven had levels >5×ULN, and six had levels >10×ULN. None of these patients had a serum bilirubin level >2 mg/dL. All 29 patients with clinical relapse were successfully retreated with NAs and achieved virological and biochemical responses within a median of 10.5 weeks after retreatment. Overall, 44 patients in the treatment-discontinuation group (60%) did not require retreatment during follow-up. No patient in this group developed cirrhosis or HCC or required hospitalization. There was no significant difference in patient characteristics between patients with and without clinical relapse (Table 4).

Quantitative HBsAg measurements at the time of NA discontinuation were available for 60 patients. No clinical relapse was observed in patients with HBsAg levels <100 IU/mL (0/5), whereas relapse occurred in 52.2% (12/23) of patients with HBsAg levels between 100 and <1000 IU/mL and in 46.9% (15/32) of those with HBsAg levels ≥1000 IU/mL (p=0.228) (Table 5).

Discussion

In the present study, we evaluated the long-term clinical outcomes of CHB following the discontinuation of NA treatment in patients with HBeAg-negative chronic hepatitis B. These patients had been treated with NA for at least five years and had achieved HBV suppression for at least the last three years preceding discontinuation. In this study, the cumulative HBsAg seroclearance rate among pa-

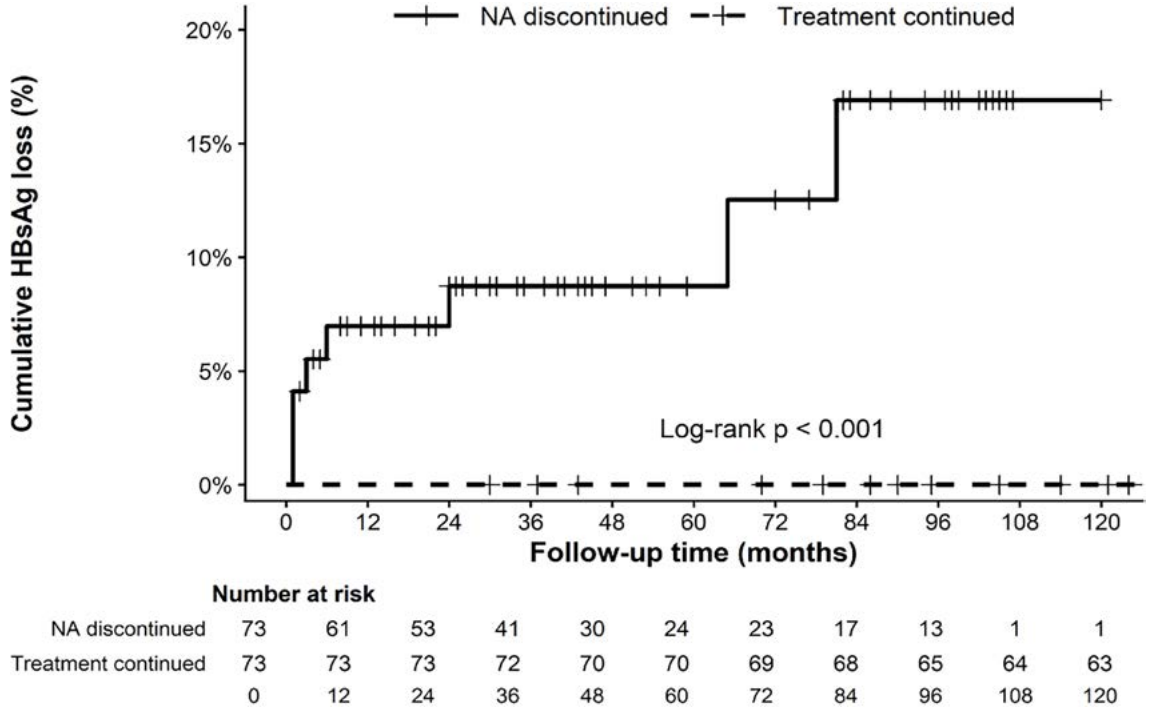


Figure 2. Kaplan–Meier curves illustrating the cumulative probability of HBsAg seroclearance in the nucleos(t)ide analogue discontinuation and continuation groups.

tients who discontinued NA treatment was 16.9% at month 120, with three-quarters of those who achieved HBsAg seroclearance also seroconverting to anti-HBs. However, none of the patients who continued NA treatment had HBsAg seroclearance. This finding confirms that previous studies have shown higher HBsAg seroclearance rates following NA cessation.[12,17–19] It also indicates that discontin-

Table 2. Characteristics of patients with and without HBsAg seroclearance in the NA discontinuation group

Characteristic	HBsAg seroclearance (n=8)	No HBsAg seroclearance (n=65)	p
Age at the index date (years)	48 (46–55)	53 (44–59)	0.572
Sex, male/female	7/1	34/31	0.072
Disease duration at the index date (months)	197.5 (168.5–212)	205 (176–228)	0.270
Serum HBV DNA (log10 IU/mL)	4.94 (3.67–6.20)	5.40 (4.00–6.80)	0.310
Serum HBV DNA >20,000 IU/mL (%)	57.1	69.0	0.672
Serum ALT (U/L)	94 (25–258)	37.5 (23–109)	0.270
Serum AST (U/L)	55 (29–124)	30 (22–74)	0.203
Serum GGT (U/L)	28 (20–56)	22 (14–32)	0.167
Total bilirubin (mg/dL)	0.70 (0.40–1.20)	0.80 (0.50–1.10)	0.773
Albumin (g/dL)	4.20 (3.90–4.30)	4.40 (4.20–4.60)	0.069
Platelet count ($\times 10^3/\mu L$)	188 (136–269)	221 (188–277)	0.186
INR	1.00 (1.00–1.10)	1.00 (0.96–1.03)	0.152
HAI on liver biopsy	8.50 (8–9)	8.00 (6–9)	0.351
Fibrosis score	1.00 (0–2.00)	1.00 (1.00–2.00)	0.700
Significant fibrosis (stage ≥2) (%)	33.3	37.8	1.000

Data are presented as median (25^{th}–75^{th} percentiles) or percentage, as appropriate. Laboratory and histological variables are pretreatment values obtained before NA initiation; age and disease duration were assessed at the index date, defined as the date of NA discontinuation. Percentages were calculated among patients with available data; denominators may vary because of missing values. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CHB: Chronic hepatitis B; GGT: Gamma-glutamyl transferase; HAI: Histological activity index; HbsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; INR: International normalized ratio; NA: Nucleos(t)ide analogue.

Table 3. Firth-penalized Cox regression analysis of HBsAg seroclearance after NA discontinuation in patients with CHB

Variable	Univariable HR (95% CI)	p	Multivariable HR (95% CI)	p
Age at NA discontinuation, <50	2.53 (0.67–10.97)	0.170	5.72 (1.26–35.01)	0.023
Sex, male vs female	3.94 (0.86–37.39)	0.081		
ALT ≥40	3.23 (0.73–19.07)	0.125		
AST ≥40	4.12 (0.96–23.53)	0.056	6.29 (1.36–39.96)	0.018
GGT ≥50	3.14 (0.56–13.32)	0.173		
HBV DNA, <20,000	1.40 (0.31–5.87)	0.647		
Liver fibrosis stage, <2	1.18 (0.26–6.80)	0.832		
HBsAg level at NA discontinuation, <1,000 IU/mL	2.60 (0.57–15.16)	0.220		

Reference ranges: ALT and AST, 0–40 U/L; GGT, 10–50 U/L. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CHB: Chronic hepatitis B; CI: Confidence interval; GGT: Gamma-glutamyl transferase; HbsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HR: Hazard ratio; NA: Nucleos(t)ide analogue.

Table 4. Characteristics of patients with and without clinical relapse after NA discontinuation

Characteristic	Clinical relapse (n=29)	No clinical relapse (n=44)	p
Age ≥50 years at NA discontinuation (%)	62.1	54.5	0.525
Male sex (%)	58.6	54.5	0.731
Pretreatment serum HBV DNA >20,000 IU/mL (%)	67.9	67.6	0.980
Pretreatment serum ALT ≥40 U/L (%)	48.3	52.5	0.729
Pretreatment serum AST ≥40 U/L (%)	41.4	42.5	0.926
Pretreatment serum GGT ≥50 U/L (%)	13.8	15.0	1.000
Significant fibrosis on pretreatment liver biopsy (stage ≥2) (%)	55.2	56.8	0.890
HBsAg seroclearance, n (%)	0 (0)	8 (18.2)	0.019

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CHB: Chronic hepatitis B; GGT: Gamma-glutamyl transferase; HbsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; NA: Nucleos(t)ide analogue.

uing long-term NA treatment can successfully lead to a functional cure in HBeAg-negative patients with CHB.

HBsAg seroclearance can occur spontaneously in individuals with chronic HBV infections over time. HBsAg seroclearance is associated with sustained immune control of HBV and better clinical outcomes.[7,10,11] Several factors, including age, gender, serum HBsAg and HBV DNA levels, HBeAg status, disease stage, the presence of hepatic steatosis, type and duration of NA therapy, and HBsAg levels at the time of NA discontinuation, affected HBsAg seroclearance.[7,10,11] We recently reported that hepatic steatosis, as documented by liver biopsy, contributes to HBsAg seroclearance in patients with chronic HBV infection.[20] Serum AST level appeared to be a more robust immunologic indicator than serum ALT level and possibly reflects greater immune-mediated hepatocellular activity relevant to functional cure.[21] In the present study, younger age and elevated pretreatment serum AST levels were significantly associated with achieving a functional cure, and this association increased over time. Additionally, nearly all patients who achieved a functional cure had low serum HBsAg levels at the time of discontinuation of NA treatment.

The immune control network of HBV infection is a complex interplay between HBV and host immunity. There is a consensus regarding

Table 5. Clinical relapse rates according to quantitative HBsAg level at NA discontinuation

Outcome	Quantitative HBsAg Titer (IU/ml)			
	<100 IU/mL (n=5)	100 to <1,000 IU/mL (n=23)	≥1,000 IU/mL (n=32)	p
Clinical relapse rate, % (n/N)	0.0 (0/5)	52.2 (12/23)	46.9 (15/32)	0.228

The analysis included 60 patients with available quantitative HBsAg measurements at NA discontinuation. HbsAg: Hepatitis B surface antigen; NA: Nucleos(t)ide analogue.

the relationship between adaptive immune responses and HBV-specific T-cell responses. Multispecific and robust HBV-specific T cells play a significant role in managing HBV infection by directly killing HBV-infected hepatocytes and through non-cytolytic degradation of HBV markers, such as cccDNA, during a self-limiting acute HBV infection.[21–23] However, HBV-specific T cell responses are often hardly detectable and non-functional in patients with CHB due to chronic antigenic overstimulation of these T cells.[21] This phenomenon is referred to as T-cell exhaustion. NA treatment can help recover T cell responses.[18,21,24,25] The extent of virological or biochemical relapse

after discontinuation of NA treatment is a key factor in triggering the immune system and achieving a functional cure.[18,21,24,25]

Virological relapse induces the production of inflammatory and antiviral cytokines, chemokines, and growth factors.[18,21,24,25] This altered cytokine milieu, along with an increased amount of HBV antigens, may act as activators of the immune response against HBV. A maximum peak level of serum HBV DNA during virological relapse and an increase in serum ALT levels are associated with subsequent HBsAg seroclearance.[18] Furthermore, after discontinuation of NA treatment, virological relapse may induce multifunctional T-cell responses in patients with CHB. Clinical relapse has therefore been proposed as a potential trigger for immune control.[18]

HBV-specific T cell responses were heterogeneous among patients with CHB. In addition to a functional cure, most patients who discontinued NA treatment achieved sustained remission after stopping treatment.[7,8] These patients had negative or low HBV DNA levels (<2000 IU/mL) and normal serum ALT levels during the follow-up period, similar to those with chronic HBV infection.

The timing of retreatment with NA in patients with clinical relapse is unclear. After the discontinuation of NA treatment, serum HBV DNA levels increased immediately. Most clinical relapse cases occurred within the first three months following treatment discontinuation, consistent with previous reports.[8,12] A virological relapse should be considered a precursor to a biochemical relapse. Notably, only half of these spikes were accompanied by serum aminotransferase elevations exceeding twice the upper limit of normal. These findings support structured monitoring after NA discontinuation, particularly during the first 24 weeks, when the risk of reactivation is highest. In the subsequent assessments conducted during the first six months after discontinuing treatment, we observed 49 virological relapses. Importantly, clinical relapses in these 29 patients were reliably controlled with NAs and responded favorably to retreatment. No serious adverse events were observed following NA retreatment.

This study involved a well-defined and homogeneous CHB patient population, with long-term follow-up and comparison to an age- and sex-matched control group. There are a few limitations that should be acknowledged. This study employed a retrospective single-center design, which may limit the generalizability of our findings. Propensity-score matching was based solely on age and sex. Additionally, quantitative HBsAg levels measured using the Roche Elecsys HBsAg II kit were not routinely available in clinical practice, hindering a more detailed analysis of virological dynamics.

Conclusion

In conclusion, the discontinuation of long-term NA treatment for non-cirrhotic, HBeAg-negative CHB patients represents a promising strategy toward achieving a functional cure. Younger age and elevated baseline serum aminotransferase levels appear to be strong indicators of a potential functional cure. Ensuring close post-discontinuation surveillance remains essential to promptly manage clinical relapses.

Ethics Committee Approval: The study protocol was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (dated May 22, 2025, and numbered 2025/393), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The authors did not have any conflicts of interest to declare.

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