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Original article

Sustained response and HBsAg loss after nucleo(s)tide analogue discontinuation in chronic hepatitis B patients: the prospective SNAP study

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ABSTRACT

Background & Aim(s): Current guidelines suggest that nucleos(t)ide analogues (NA) can be discontinued before HBsAg loss in a selected group of chronic hepatitis B (CHB) patients. We aimed to study the safety and off-treatment response after NA cessation.

Methods: This is a prospective, multicentre, cohort study in which eligible patients discontinued NA therapy. Adult patients, with a CHB mono-infection, HBeAg-negative, without a (history of) liver cirrhosis, who had achieved long-term viral suppression were eligible. Follow-up visits were planned at week 2-4-8-12-24-36-48-72-96. Re-treatment criteria included severe hepatitis (ALT >10x ULN), signs of imminent liver failure (bilirubin >1.5x ULN or INR >1.5), or at the physician's own discretion.

Results: In total, 33 patients were enrolled. Patients were predominantly Caucasian (45.5%) and had genotype A/B/C/D/unknown in 3/4/6/10/10 (9.1/12.1/18.2/30.3/30.3%). At week 48, 15 patients (45.5%) achieved a sustained response (HBV DNA <2,000 IU/mL). At week 96, 13 patients (39.4%) achieved a sustained response, 4 (12.1%) achieved HBsAg loss, and 12 (36.4%) were re-treated. Severe hepatitis was the main reason for re-treatment (n=7, 21.2%). One patient with severe hepatitis developed jaundice, without signs of hepatic decompensation. Re-treatment was successful in all patients.

Conclusion: NA therapy can be ceased in a highly selected group of CHB patients if close follow-up can be guaranteed. Treatment cessation may increase the chance of HBsAg loss in selected patients, which is counterbalanced by a significant risk of severe hepatitis.

Introduction

Viral hepatitis B is considered a global public health threat with 296 million infected individuals [1]. Patients with a chronic hepatitis B (CHB) infection are at risk to develop liver cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC) [1]. Viral suppression or eradication halts further progression of the liver disease and improves life expectancy [2,3].

First-line therapy includes nucleos(t)ide analogues (NA), which suppress HBV DNA replication by inhibiting the HBV reverse transcriptase. NA therapy can achieve long-term viral suppression in the majority of patients [4]. However, functional cure (loss of hepatitis B surface antigen [HBsAg]) is rare during antiviral treatment. Therefore, lifelong continuous treatment has been the backbone of antiviral management in many CHB patients [4].

A growing interest has risen in finite NA therapy. Several studies

Abbreviations: HBV, hepatitis B virus; CHB, Chronic hepatitis B; HCC, hepatocellular carcinoma; NA, nucleos(t)ide analogues; HBsAg, hepatitis B surface antigen; EASL, European Association for the study of the Liver; HBeAg, hepatitis B e antigen; IU/mL, international units/mililitre; HIV, human immunodeficiency virus; ALT, alanine aminotransferase; LLOQ, lower limit of quantification; RCT, randomised controlled trial; INR, international normalized ratio; U, units; IU, international units; L, litre, mL, mililitre; µmol, micromol; g, gram.

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demonstrated that a substantial proportion of patients achieved favourable off-treatment outcomes such as durable viral suppression (sustained response) and even HBsAg loss [5–8]. Currently, the guideline of the European Association for the study of the Liver (EASL) for hepatitis B suggests that NA therapy cessation may be considered in a selected group of patients, including HBeAg-negative patients without signs of cirrhosis and those who have achieved long-term on-treatment viral suppression and HBeAg positive patients who have achieved HBeAg seroconversion [4].

In this study, we aimed to assess the safety and off-treatment outcomes in a cohort of CHB patients that discontinued NA therapy.

Patients and methods

Study design

This is a prospective, multicentre cohort study in which eligible patients with CHB discontinued NA therapy. The study has been approved by the medical ethical committee and is in line with the principles of the Declaration of Helsinki of 1975 and Good Clinical Practice guidelines. In addition, patient selection and follow-up were in line with the current EASL guideline [4].

Study population

Adult patients with a chronic HBeAg-negative hepatitis B (CHB) infection were enrolled. Inclusion criteria comprised treatment with entecavir or tenofovir (disoproxil or alafenamide), and a liver stiffness measurement (using Fibroscan®, Echosens, France) of <7.0 kPa at baseline (within 6 months before screening). Patients must have achieved long-term viral suppression (HBV DNA <80 IU/mL). The duration of viral suppression depended on the HBeAg-status at the time of NA initiation: Among previously HBeAg-positive patients, consolidation therapy must be at least 12 months after a stable HBeAg seroconversion (confirmed HBeAg seroconversion at least 6 months apart). Among HBeAg-negative patients, consolidation therapy must be at least 3 years. Exclusion criteria included a history of cirrhosis based on liver biopsy (METAVIR F4) or liver stiffness measurement (≥12.5 kPa), history of hepatic decompensation, (history of) hepatocellular carcinoma, other active malignancy, (planned) treatment with immunosuppressive agents, (planned) pregnancy, co-infection with human immunodeficiency virus (HIV), hepatitis C or hepatitis D, a concomitant liver condition that may influence liver chemistry (defined as ALT >2x upper limit of normal [ULN] and/or bilirubin >1x ULN), other indication for continued NA therapy, expected non-compliance to follow-up, treatment with medication that increases INR (such as vitamin K antagonist), unwillingness to refrain from sexual activity without a condom with partners not vaccinated against HBV.

Study assessments

Study visits were planned at weeks 2, 4, 8, 12, 24, 36, 48, 72, and 96 after treatment discontinuation. Additional study visits were planned in case of an increase in ALT or HBV DNA levels, at the own discretion of the treating physician. At every study visit, a clinical assessment and a full laboratory assessment was performed including liver enzymes, HBV DNA, HBeAg, anti-HBe, and HBsAg levels. In addition, liver stiffness measurements were also performed at the last study visit (week 96).

Re-treatment criteria

Re-treatment was initiated if the patient experienced a severe hepatic flare (ALT >10x ULN) or had signs of imminent liver failure (bilirubin >1.5x ULN and/or INR >1.5). Treatment could also be recommenced at the treating physician's discretion, for instance in case of an HBeAg seroreversion or persistent ALT flare (for weeks ALT levels between 5 and 10x the ULN with persistent high HBV DNA load).

Endpoints

The main study endpoint included the achievement of a sustained response, defined as HBV DNA <2,000 IU/mL at week 48 after therapy discontinuation. Secondary study endpoints included sustained response at week 96 after therapy discontinuation, need for re-treatment (according to study protocol or treating physician), HBsAg clearance at week 48 and 96, the occurrence of a virological relapse (HBV DNA > 2,000 IU/mL) or combined relapse (HBV DNA > 2,000 IU/mL and ALT > 2x ULN), the occurrence of signs of liver failure (bilirubin >1.5x ULN and/or INR >1.5), the relationship between sustained response at week 48 and 96 and serum levels of HBsAg at the time of treatment cessation, ALT levels at week 48 and 96, Liver stiffness (Fibroscan) value at week 96.

Laboratory measurements

Serum HBV DNA, HBeAg, anti-HBe, quantitative HBsAg levels, liver enzymes, platelet count and INR were measured at the screening visit and at every visit during follow-up. HBV DNA was quantified by automated techniques at the participating centres, with a lower limit of quantification (LLOQ) of 20 IU/mL. Quantification of HBsAg was performed using Liaison XL Murex HBsAg Quant (Diasorin, Saluggia, Italy) with a LLOQ of 0.05 IU/mL. Liver enzymes, platelet count and INR tests were performed by automated techniques at the participating centres.

Statistical analysis

Descriptive data were described as numbers (with percentages), medians (with interquartile range; IQR) and means (± standard deviation; SD). To assess predictors for off-treatment outcome, chi-squared test was used to compare categorical variables, whereas a one-way ANOVA was used to compare HBsAg decline among patients with a sustained response, HBsAg loss or severe hepatitis at week 96. Differences were considered statistically significant when $p<0.05$. HBsAg levels at baseline were stratified by ethnicity as proposed by the paper of Hirode *et al.* [9]; Asian <100 IU/mL and Caucasian (and other ethnicities) <1,000 IU/mL. IBM SPSS for Windows version 28.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. GraphPad Prism version 5 for Windows (GraphPad Software, San Diego, California, USA) was used for graphical representation of the results.

Results

Patients

In total, we included 33 patients. Baseline patient characteristics are displayed in Table 1. Patients were predominantly male (72.7%), Caucasian (45.5%), and had genotype A/B/C/D in 3/4/6/10/10 (9.1/12.1/18.2/30.3/30.3%). Most patients were treated with entecavir (51.5%) and were HBeAg-negative at the start of NA therapy (90.9%). Mean baseline HBsAg levels were 2.63 log IU/mL (±0.88).

Off-treatment follow-up

During off-treatment follow-up, the first viral relapses were observed in week 4; nine patients (28.1%) had HBV DNA levels > 2,000 IU/mL.

At week 48, 15/33 patients (45.5%) achieved a sustained response, and 12 patients (36.4%) had been re-treated (Fig. 1). Severe hepatitis was the most common re-treatment reason (7/12 patients, 58.3%, Table 2). In total, 25/33 patients (75.8%) experienced a virological relapse within the first 48 weeks. Among those 25 patients, 12 patients (48.0%) experienced a combined relapse (HBV DNA > 2,000 IU/mL and ALT > 2x ULN).

Table 1
Patient characteristics.

	n = 33
Age at inclusion (years; mean ±SD)	48 (±9)
Sex (male; n,%)	24 (72.7)
Ethnicity (n,%)	
Caucasian	15 (45.5)
Asian	10 (30.3)
Black	6 (18.2)
Other	2 (6.1)
HBV genotype (n,%)	
A	3 (9.1)
B	4 (12.1)
C	6 (18.2)
D	10 (30.3)
Unknown	10 (30.3)
HBeAg-status at NA initiation (n,%)	
HBeAg-positive	3 (9.1)
HBeAg-negative	30 (90.9)
NA regime (n,%)	
ETV	17 (51.5)
TDF	13 (39.4)
TAF	3 (9.1)
Previous antiviral treatment (n,%)	
No	13 (39.4)
Other NA	8 (24.2)
PEG-IFN	4 (12.1)
NA + PEG-IFN	8 (24.2)
Duration NA therapy (weeks; median, IQR)	450 (319-588)
Laboratory measurements	
HBsAg (log IU/mL, mean, SD; range)	2.63 (±0.88; 0.11-3.98)
ALT (U/L; median, IQR; range)	25 (18-33; 12-54)
Liver stiffness measurements (kPa; mean, ±SD)	4.7 (±1.06)

[1]at NA initiation.
Abbreviations: HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; ETV, entecavir; TDF, tenofovir disoproxil; TAF, tenofovir alafenamide; NA, nucleos(t)ide analogues; PEG-IFN, pegylated interferon; HBsAg, hepatitis B surface antigen; ALT, alanine aminotransferase; IU, international units; U, units; mL, mililitre.

At week 96, 13 patients (39.4%) achieved a sustained response, and 12 patients (36.4%) were re-treated (Fig. 1, Table 2). HBsAg loss was observed in 4 patients (12.1%).

The mean decline in HBsAg levels was 0.69 log IU/mL (±1.75), and 1.00 log IU/mL (±1.35) at weeks 48, and 96 respectively. Among patients that achieved sustained response and HBsAg loss at week 96, HBsAg decline was 0.56 log IU/mL (±0.68) and 3.72 log IU/mL (±0.51) at week 96. None of the patients who achieved HBsAg loss experienced an ALT flare. However, among patients that experienced severe hepatitis, HBsAg decline was 1.45 log IU/mL (±1.06) at week 96 (versus 0.86 log IU/mL [±1.30] among HBsAg positive subjects without severe hepatitis; p = 0.174). In Fig. 2, the kinetics of HBsAg, HBV DNA and ALT levels are depicted of three patients with a severe hepatitis that experienced an HBsAg decline of ≥ 2.0 log IU/mL at week 96.

Factors assessed for predicting outcome are depicted in Table 3. In these selected patients there were no significant differences between patients achieving sustained response or HBsAg loss or those experiencing a severe hepatic flare. However, although statistical significance was not reached, when HBsAg levels at baseline were stratified based on ethnicity, we observed that the patients with low baseline HBsAg levels had a higher probability of sustained response (57.1%) and HBsAg loss (21.4%), and lower risk of severe hepatitis (7.1%, Fig. 3).

Safety

Severe hepatitis was observed in seven patients (21.2%), all occurred within the first year. These patients were re-treated in line with the study protocol. The first severe hepatitis was observed at week 10, and the last severe hepatitis at week 30. One patient experienced an HBeAg-seroreversion, which converted to HBeAg-negative after re-treatment was started. Complete viral suppression was achieved in all re-treated patients. In the whole study group, median ALT levels were 29 U/L (22-41) at week 48 and 26 U/L (18-35) at week 96.

One patient with severe hepatitis developed jaundice (bilirubin 58 μmol/L), without any signs of hepatic decompensation (normal INR levels, no encephalopathy). He was successfully re-treated. Two patients were admitted to the hospital, but not related to the study intervention; one patient was admitted due to a covid-19 infection, and one patient because of a stroke. Both of the patients recovered and none of the included patients died.

Discussion

In this prospective study, we showed that NA discontinuation in highly selected patients leads to sustained response in 39% and HBsAg loss in 12% of the patients after two years of follow-up. However, a

Table 2
Retreatment reasons.

Patient	Week	Retreatment reason	NA regime
1004	9	patient preference	TDF
1007	11	HBeAg seroreversion	TDF
1010	11	Severe hepatitis	TDF
1012	2	Start immunosuppression[1]	ETV
1013	6	patient preference	ETV
1018	48	Persistent flare	TDF
1022	23	Severe hepatitis	ETV
1024	30	Severe hepatitis	ETV
1027	13	Severe hepatitis	TAF
1031	13	Severe hepatitis	TAF
2002	24	Severe hepatitis	ETV
3003	10	Severe hepatitis	TDF

Severe hepatitis was defined as an ALT level >10x ULN.
Abbreviations: TDF, tenofovir disproxil; ETV, entecavir; TAF tenofovir alafenamide.
[1] Start methotrexate for the treatment of rheumatoid arthritis

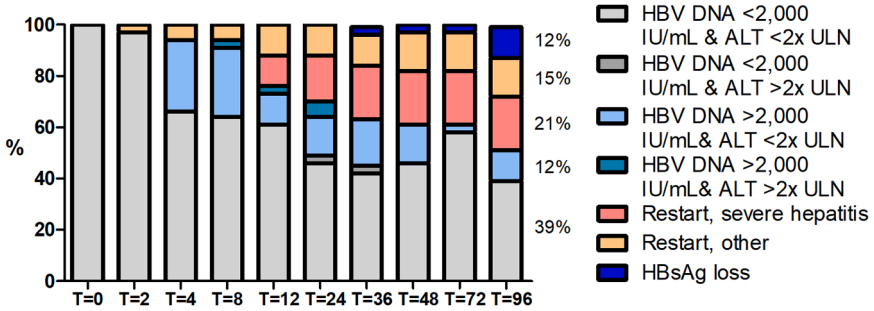

Fig. 1. Off-treatment outcome.
Severe hepatitis was defined as an ALT level >10x ULN.
Abbreviations: HBV, hepatitis B virus; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; IU, international units; mL, millilitre.

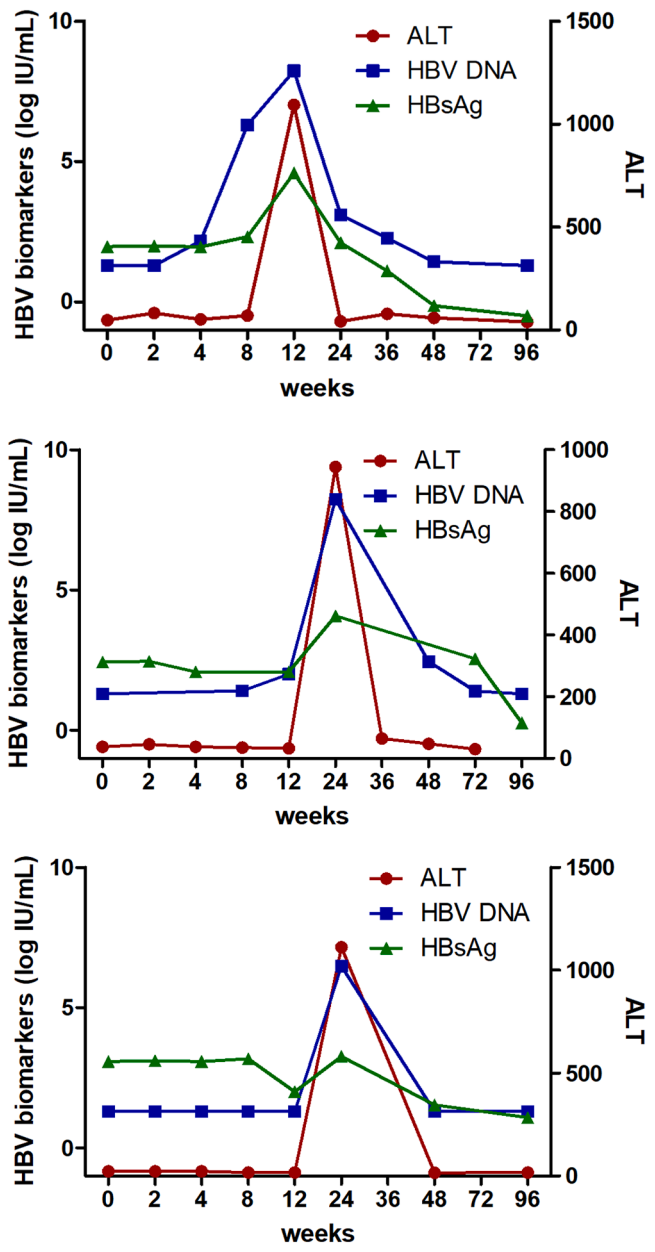

Fig. 2. Kinetics of HBsAg, HBV DNA and ALT levels among patients with a severe hepatitis and HBsAg decline of ≥ 2.0 log IU/mL at week 96 off-treatment.
Severe hepatitis was defined as an ALT level >10x ULN.
Abbreviations: HBV, hepatitis B virus; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; IU, international units; mL, millilitre.

virological relapse was observed in the majority of patients and 21% of the patients experienced severe hepatitis. None of the patients experienced hepatic decompensation or died, and re-treatment was successful in all patients. Thus, NA can be safely discontinued in a highly selected group of HBeAg-negative hepatitis B patients if close follow-up can be guaranteed.

HBsAg loss rate in our study was much higher compared to the expected rate of ~1% among patients who continue NA therapy [10,11]. Our week 96 follow-up data are in line with a randomised controlled trial (RCT) executed in Germany (FINITE study), where HBsAg loss was achieved in 14% of the patients who stopped NA therapy compared to 0% of the patients that remained on-NA therapy [10]. However, another RCT (Toronto STOP study) showed no difference in HBsAg rates among patients that stopped or continued NA therapy [12]. These differences in

Table 3
Predictors for off-treatment outcomes at week 96.

	Sustained response[1] (n=13)	HBsAg loss (n=4)	Severe hepatitis[2] (n=7)	Other[4] (n=9)	p-value[5]
Age at inclusion (years; mean ±SD)	50 (±10)	50 (±3)	45 (±5)	47 (±11)	0.728
Sex (male; n,%)	10 (76.9)	4 (100)	5 (71.4)	5 (55.6)	0.398
Ethnicity (n,%)					0.824
Caucasian	6 (46.2)	2 (50.0)	3 (42.9)	4 (44.4)	
Asian	3 (23.1)	1 (25.0)	3 (42.9)	3 (33.3)	
Black	3 (23.1)	0 (0)	1 (14.3)	2 (22.2)	
Other	1 (7.7)	1 (25.0)	0 (0)	0 (0)	
HBV genotype					0.981
(n,%)	2/8 (25.0)	0 (0)	0/4 (0)	1/7	
A	1/8 (12.5)	1 (25.0)	1/4 (25.0)	(14.3)	
B	2/8 (25.0)	1 (25.0)	1/4 (25.0)	1/7	
C	3/8 (37.5)	2 (50.0)	2/4 (50.0)	(14.3)	
D				2/7	
				(28.6)	
				3/7	
				(42.9)	
HBeAg-status[1] (n,%; HBeAg negative)	13 (100)	3 (75.0)	6 (85.7)	8 (88.9)	0.424
NA regime (n,%)					0.864
ETV	7 (53.8)	2 (50.0)	3 (42.9)	5 (55.6)	
TDF	4 (30.8)	2 (50.0)	3 (42.9)	4 (44.4)	
TAF	2 (15.4)	0 (0)	1 (14.3)	0 (0)	
Laboratory measurements HBsAg (log IU/mL, mean, SD)	2.50 (±0.98)	2.12 (±0.51)	2.80 (±0.57)	3.0 (±0.89)	0.316

[3]HBeAg-status at NA initiation.
Abbreviations: HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; ETV, entecavir; TDF, tenofovir disoproxil; TAF, tenofovir alafenamide; NA, nucleos(t)ide analogues; PEG-IFN, pegylated interferon; HBsAg, hepatitis B surface antigen; ALT, alanine aminotransferase; IU, international units; U, units; mL, mililitre.
[1] Sustained response was defined as HBV DNA <2000 IU/mL.
[2] Severe hepatitis was defined as an ALT level >10x ULN.
[4] Including patients with elevated HBV DNA levels (>2,000 IU/mL), or re-treatment because of other reasons than severe hepatitis.
[5] using chi-quare test for categorical variables and one-way ANOVA for continuous variables.

HBsAg loss could be explained by differences in ethnicity between these studies; predominantly Caucasian in the FINITE study and our study, and mainly Asians in the Toronto STOP study. Emerging evidence suggests that Asian patients have a lower probability of HBsAg loss compared to Caucasian [9], possibly due to genetic differences, HBV genotype, or duration of the infection. Another explanation for our high HBsAg loss rate might be the differences in HBeAg-status at the start of NA therapy. Our study and the FINITE study included respectively 90% and 100% of the patients who were HBeAg-negative at the start of NA therapy, compared to 60% of the patients in the Toronto STOP study. Contradicting data have been published about whether HBeAg-status influences off-treatment outcome, although a large pooled analyse showed no effect of HBeAg-status [9,13,14]. Finally, albeit not exactly the same, criteria were comparable between our study and the FINITE or Toronto STOP study; i.e. patients were allowed to experience a viral relapse and mild elevation in liver enzymes, but required re-treatment in case of profound increase in ALT.

We observed severe hepatic flares among 21% of the patients. One patient experienced jaundice without other signs of hepatic decompensation. It has been well described that the majority of patients experience HBV reactivation after NA cessation, which leads to an ALT flare in a proportion of patients [15,16]. Interestingly, it has been demonstrated that the absence of flares correlated with the presence of functional T cells, suggesting immune control in this population [17].

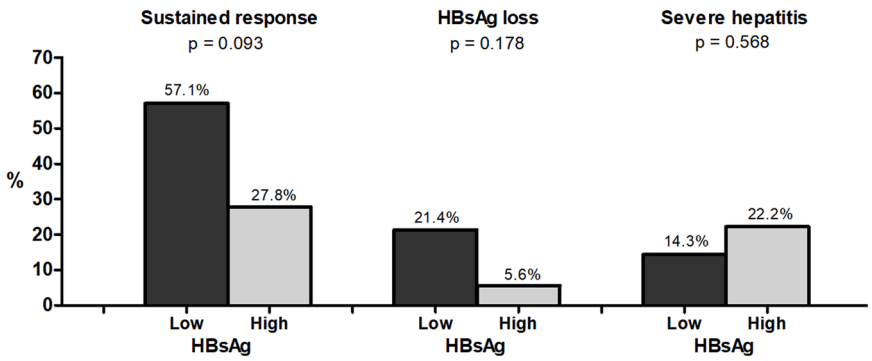

Fig. 3. Off-treatment outcomes based on HBsAg level at end-of-treatment.
Chance of the outcome of sustained response (HBV DNA <2,000), HBsAg loss, or severe hepatitis (ALT <10x ULN) at week 96 post-treatment among patients with low (<100 among Asian and <1,000 among other ethnicities) versus high (>100 among Asian and >1,000 among Caucasian other ethnicities) HBsAg levels. Abbreviations: HBsAg, hepatitis B surface antigen.

However, many patients with an ALT flare did not achieve HBsAg loss. Instead, they are at risk for hepatic decompensation and sometimes death [5,18,19]. Therefore, extensive discussion with the patient and his family on the proposed risks and benefits of the treatment plan as well as close off-treatment follow-up is crucial.

In this study, we observed that patients with severe hepatitis experienced a more profound HBsAg decline at week 96, compared to patients with a sustained response. One possible explanation could be the reduced intrahepatic HBV reservoir due to the host's immune attack. However, most flares occurred in the first (half) year and HBsAg decline was observed after two years. Whether these events can be linked is unknown and warrants confirmation in other studies. In addition, we did observe that patients with low HBsAg levels at the end of NA treatment might be more likely to achieve HBsAg loss. In line with the paper by Hirode *et al.*, [9] we observed that 21% of the Caucasians with HBsAg <1,000 IU/mL or Asians <100 IU/mL achieved HBsAg loss.

Strengths of this study include the prospective design with strict inclusion criteria and close off-treatment follow-up guidance. Also, our cohort included a multi-ethnic population. However, some limitations need to be mentioned. First, due to the limited number of patients included in this study, we lacked the power to find any predictors for off-treatment outcomes. Also, we did not have access to study serum biomarkers such as HBV RNA and HBcrAg as potential predictors. Finally, although the majority of flares occurred in the first year of follow-up, the study duration of two years might be too short to study long-term HBsAg loss and change in HCC risk.

In conclusion, the findings in our study support the concept that NA can be ceased, but only in a highly selected group of patients who are willing to comply with strict monitoring. Treatment cessation may increase the chance of HBsAg loss, but patients also have a significant risk of severe hepatic flares.

CRediT authorship contribution statement

Sylvia M. Brakenhoff: Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft. **Mark Claassen:** Data curation, Writing – review & editing. **Pieter Honkoop:** Data curation, Writing – review & editing. **Robert J. de Knegt:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing. **Annemiek A. van der Eijk:** Resources, Writing – review & editing. **André Boonstra:** Investigation, Methodology, Resources, Writing – review & editing. **Robert A. de Man:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Milan J. Sonneveld:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Supervision, Validation, Visualization, Writing – original draft.

Declaration of Competing Interest

AB has received research grants from GSK, Gilead Sciences, Fujirebio, and Janssen. RdK has received honoraria for consulting/speaking from Gilead, Janssen, Echosens, AbbVie, and Norgine and received research grants form Gilead, GSK and Janssen. MS has received speaker's fees and research support from Roche, Innogenetics, BMS, Gilead and Fujirebio. The other authors report no disclosures.

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