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Discontinuation of Oral Antivirals in Chronic Hepatitis B: A Systematic Review

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The possibility of safe discontinuation of therapy with nucleos(t)ide analogues (NAs) remains one of the most controversial topics in the management of chronic hepatitis B. Therefore, we systematically reviewed the existing data on NA discontinuation in this setting and tried to identify factors affecting the probability of posttherapy remission. A literature search was performed in order to identify all published studies including patients who discontinued NAs in virological remission (VR) and were followed for ≥12 months thereafter. Twenty-five studies with 1716 patients were included. The pooled rates of durable VR remission were 51.4%, 39.3%, and 38.2% at 12, 24, and 36 months, respectively, after NA discontinuation, being relatively higher in initially hepatitis B e antigen (HBeAg)–positive patients (62.5%, 53.4%, 51.5%) than HBeAg-negative patients (43.7%, 31.3%, 30.1%) ($P = 0.064$). The weighted probability of durable biochemical remission was 65.4%, being numerically higher in HBeAg-positive than HBeAg-negative patients (76.2% versus 56.7%, $P = 0.130$). The weighted probability of hepatitis B surface antigen loss was 2.0%. The rates of durable VR did not significantly differ according to the VR definition (hepatitis B virus DNA <200, <2000, <20,000 IU/mL) or duration of on-therapy VR in HBeAg-positive patients, but they were significantly higher in studies with HBeAg-negative patients and on-therapy VR > 24 than ≤ 24 months (VR at 12 months off-NAs: 75.0% versus 35.6%, $P = 0.005$). The weighted probability of durable HBeAg seroconversion was 91.9% and 88.0% at 12 and 24 months, respectively, after NA discontinuation without being affected by the duration of on-therapy VR or consolidation therapy (>6 months in all studies). *Conclusion*: Durable VR seems to be feasible in a substantial proportion of patients who discontinue long-term NA therapy; on-therapy VR > 24 months offers higher chances of off-NA VR in patients with HBeAg-negative chronic hepatitis B. (HEPATOLOGY 2016;63:1481-1492)

Treatment against hepatitis B virus (HBV) has dramatically improved over the last 15 years, but HBV eradication remains a rarely attainable target.[1-3] Pegylated interferon-alfa therapy given for a finite duration of usually 48 weeks can achieve sustained off-therapy responses, with almost half of the responders clearing hepatitis B surface antigen (HBsAg) in the long term. However, only 20%-30% of patients with hepatitis B e antigen (HBeAg)–positive or HBeAg-negative chronic hepatitis B (CHB) may achieve sustained off-therapy responses after a course of pegylated interferon-alfa.[1-3] Many patients are reluctant to start treatment with this agent because interferon-alfa may have severe side effects as well as an unfavorable safety profile. Thus, oral antiviral agents, nucleos(t)ide analogues (NAs), represent the main therapeutic option for the majority of CHB patients.[4]

Abbreviations: ALT, alanine aminotransferase; BR, biochemical remission; CHB, chronic hepatitis B; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, nucleos(t)ide analogue; ULN, upper limit of normal; VR, virological remission.

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Although there were reasonable concerns because of increasing rates of viral resistance with the use of the first-generation and second-generation oral antivirals, particularly lamivudine, the probability of HBV resistance is negligible (0%-1%) during long-term monotherapy with the currently recommended oral agents entecavir and tenofovir.[1-3] Entecavir or tenofovir monotherapy has been shown to achieve inhibition of HBV replication in almost all adherent patients. These drugs ameliorate liver fibrosis and can reverse cirrhosis in the majority of patients.[5,6] In addition, they eventually improve morbidity and mortality of treated patients.[1,2] All NAs have an excellent tolerance and a good safety profile, but they cannot achieve HBV eradication or at least HBsAg loss in the vast majority of cases.[1,2] This is why they should be given for very long periods, perhaps indefinitely, especially in the subgroup of HBeAg-negative patients.[1,2,4] The need for long-term NA therapy raises safety issues for some patients (e.g., elderly patients with comorbidities like diabetes and renal insufficiency) and family planning issues in patients of reproductive age along with increases in treatment costs. For these reasons, many physicians treating CHB patients with NAs for years have become interested in investigating the need for continuation as well as the safety of therapy withdrawal. Several groups have started discontinuing NAs after variable durations of treatment, but no definite conclusion has been reached as of yet. Limitation of long-term duration of NA therapy seems to be one of the major aims nowadays as long as there is no realistic option to eradicate HBV in a chronic carrier within the next few years.[7]

Therefore, the aim of this review was to systematically evaluate the existing data on NA discontinuation in patients with HBeAg-positive or HBeAg-negative CHB and to potentially identify factors associated with maintenance of posttherapy remission. This systematic review was prepared according to widely accepted recommendations.[8]

Materials and Methods

SEARCH STRATEGY

The Medline/Pubmed database was searched from 2002 to December 2014 to identify all medical literature included under the search text terms "hepatitis B" and "antiviral" or "therapy" or "treatment" or "lamivudine" or "adefovir" or "entecavir" or "telbivudine" or "tenofovir" and "end" or "discontinuation" or "withdrawal." In addition, a manual search of all relevant review articles and of the retrieved original studies was performed.

All studies published in English as full papers were included if they fulfilled all of the following criteria: (1) they were observational studies (cohort or case-control) or randomized trials, (2) they included adult patients with CHB including compensated cirrhosis who discontinued oral antiviral(s) in virological remission (VR) defined by HBeAg seroconversion for initially HBeAg-positive patients and undetectable HBV DNA for all patients, (3) the duration of therapy was >12 months and that of posttherapy follow-up ≥ 12 months, (4) they provided data on the number of patients who remained in VR after treatment discontinuation, and (5) posttreatment VR was defined by serum HBV DNA levels $<100{,}000$ cp/mL or $< 20{,}000$ IU/mL. Studies including patients with HBV and hepatitis D or C and/or human immunodeficiency virus coinfection(s), hepatocellular carcinoma, liver transplantation, or treatment with only nonlicensed oral antivirals (e.g., clevudine) were excluded.

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TABLE 1. Main Characteristics of Studies Including CHB Patients Who Discontinued NAs

Reference	All Patients (n)	Patients Off-NAs, All/In VR (n)				Age (Years)	Males (n)	Race	Before NAs		Type of NAs
		Total	HBeAg$^+$	HBeAg$^-$	Cirrhosis				ALT*	HBV DNA†	
Fung et al.[10]	50	27/27	0	27/27	7	45	40	Asian	92	7.0	LAM
Enomoto et al.[11]	22	22/16	0	22/16	3	49	15	Asian	85/203	6.1/7.1	LAM
Yeh et al.[12]	71	71/71	71/71	0	11	41	55	Asian	NR	NR	LAM
Fung et al.[13]	101	22/14	22/14	0	NR	28	16	Asian	176	9.0	LAM
Wang et al.[14]	125	125/125	125/125	0	0	26/32	95	Asian	218/243	7.3/7.2	LAM‡
Kuo et al.[15]	401	124/124	124/124	0	NR	NR	NR	Asian	NR	NR	LAM
Cai et al.[16]	17	11/7	11/7	0	NR	29	12	Asian	178	9.0	TBV
Liu et al.[17]	61	61/61	0	61/61	0	32	50	Asian	194	6.5	LAM‡
Jung et al.[18]	36	19/19	10/10	9/9	4	37	12	Asian	394	7.8	ADV
Chan et al.[19]	53	53/53	0	53/53	18	56	43	Asian	117	6.5	LAM
Chaung et al.[20]	39	39/39	39/39	0	NR	34	24	Asian	139	7.7	LAM 15, ADV 14, ETV 10
Hadziyannis et al.[21]	47	33/33	0	33/33	0	53	38	Caucasian	109	7.3	ADV
Ha et al.[22]	145	145/145	0	145/145	NR	33	101	Asian	224	7.0	ADV
Song et al.[23]	48	48/48	48/48	0	0	42	29	Asian	198	8.5	ETV 31, CLE 17
He et al.[24]	66	66/66	0	66/66	0	35	50	Asian	NR	5.5	LAM 15, ADV 42, ETV 7, TBV 2
Kim et al.[25]	45	45/45	0	45/45	9	45	33	Asian	239	7.1	LAM 14, ADV 6, ETV 25
Jeng et al.[26]	95	95/95	0	95/95	39	52	83	Asian	158	6.8	ETV
Kwon et al.[27]	72	16/16	NR	NR	NR	NR	NR	Asian	NR	NR	LAM
Ridruejo et al.[28]	169	35/35	33/33	2/2	0	NR	NR	Caucasian	NR	NR	ETV
Sohn et al.[29]	95	95/95	41/41	54/54	44	47	53	Asian	196	7.3	LAM 15, ETV 67, CLE 13
Patwardhan et al.[30]	33	33/33	0	33/33	0	42	24	Mixed	65	5.3	LAM 3, ADV 14, ETV 4, TDF 12
He et al.[31]	97	97/97	97/97	0	NR	26	53	Asian	132	7.0	LAM 28, ADV 35, ETV 16, TBV 18
Chen et al.[32]	188	188/188	83/83	105/105	12	38/49	143	Asian	572/581	7.0/5.7	LAM
Jiang et al.[33]	72	72/72	33/33	39/39	8	36	53	Asian	NR	NR	LAM 24, LAM+ADV 4, ADV 21, ETV 14, TBV 9
Seto et al.[34]	184	184/184	0	184/184	34	54	125	Asian	NR	5.4	ETV

*Median ALT in international units per milliliter.
†Median HBV DNA in $\log_{10}$ copies per milliliter.
‡LAM was given in combination with interferon-alfa for 6 months in 62 patients of the study by Wang et al.[14] and 13 patients of the study by Liu et al.[17]
Abbreviations: ADV, adefovir dipivoxil; CLE, clevudine; ETV, entecavir; LAM, lamivudine; NR, not reported; TBV, telbivudine; TDF, tenofovir disoproxil fumarate.

TABLE 2. Treatment Characteristics in Studies Including CHB Patients Who Discontinued NAs

Reference	Treatment Duration (Months)	Duration of VR Before NA Cessation (Months)	Duration of HBeAg Seroconversion Before NA Cessation* (Months)	Follow-Up After NA Cessation (Months)	Definition of Durable Off-Therapy VR	Definition of Durable Off-Therapy BR†
Fung et al.[10]	24	11	—	18	HBV DNA < 200 copies/mL	ALT < ULN[d]
Enomoto et al.[11]	NR	12 or 24	—	48	HBV DNA < 100,000 cp/mL	ALT < 2 × ULN[d]
Yeh et al.[12]	NR	12	6-12	15	HBV DNA < 10,000 cp/mL	ALT < 2 × ULN[d]
Fung et al.[13]	74	25	25	20	No increase of HBV DNA >1 log cp/mL	ALT < 2 × ULN[d]
Wang et al.[14]	24 or 36	21 or 33	16 or 0	24	HBV DNA < 10,000 cp/mL	NR
Kuo et al.[15]	14	<12	8	>12	HBV DNA < 100,000 cp/mL and HBeAg-negative	ALT < ULN[d]
Cai et al.[16]	24	17	17	22	HBV DNA < 300 cp/mL and HBeAg-negative	ALT < ULN[d]
Liu et al.[17]	27	24	—	15	HBV DNA < 10,000 cp/mL	ALT < ULN[a]
Jung et al.[18]	33	18	18	12	HBV DNA < 100,000 cp/mL	ALT < ULN[d]
Chan et al.[19]	27	12-24	—	47	HBV DNA < 200 IU/mL	NR
Chaung et al.[20]	21	12-24	12	14	HBV DNA < 100 IU/mL	ALT < 2 × ULN[a]
Hadziyannis et al.[21]	56	45	—	69	HBV DNA < 2000 IU/mL	ALT < ULN[d]
Ha et al.[22]	26	24	—	16	HBV DNA < 10,000 cp/mL	ALT < ULN[a]
Song et al.[23]	26	10	10	18	HBV DNA < 300 cp/mL and HBeAg-negative	ALT < ULN[a]
He et al.[24]	37	34	—	17	HBV DNA < 2000 IU/mL	ALT < ULN[a]
Kim et al.[25]	38	18	—	26	HBV DNA < 2000 IU/mL	ALT < 2 × ULN[d]
Jeng et al.[26]	24	15	—	>12	HBV DNA < 2000 IU/mL	ALT < 2 × ULN[b]
Kwon et al.[27]	79	>24	35	32	HBV DNA < 350 IU/mL and HBeAg-negative	ALT < ULN[d]
Ridruejo et al.[28]	42	>24	>12	15	HBV DNA < 2000 IU/mL	ALT < ULN[d]
Sohn et al.[29]	22	14	14‡	22	HBV DNA < 60 IU/mL	NR
Patwardhan et al.[30]	64	54	—	36	HBV DNA < 2000 IU/mL	ALT < 1.25 × ULN[d]
He et al.[31]	35	22	18	32	HBV DNA < 2000 IU/mL and HBeAg-negative	ALT < ULN[a]
Chen et al.[32]	20 or 22	10 or 14	12	49	HBV DNA < 2000 IU/mL	NR
Jiang et al.[33]	33	12	12	13	HBV DNA < 10,000 cp/mL	ALT < ULN[d]
Seto et al.[34]	37	12	—	12	HBV DNA < 2000 IU/mL	ALT < ULN[c]

*Only for studies with HBeAg-positive patients.
†ULN of ALT: [a]40 IU/L, [b]36 IU/L, [c]58/36 IU/L for males/females, [d]not provided.
‡Months for HBeAg loss before NA cessation.
Abbreviation: NR, not reported.

The literature search was performed by two independent reviewers (I.V., K.W.), who determined which studies could be potentially included. Two lists of selected papers were compared for concordance and discrepancies, discussed, and, if necessary, arbitrated by a third reviewer (G.P.). Each study in the list of selected papers was evaluated by two independent reviewers (G.P., I.V.) in order to determine whether it fulfilled all the inclusion criteria. Two independent reviewers (I.V., E.C.) extracted data from the selected papers according to a predefined form. Data discrepancies and potential queries were arbitrated by a third reviewer (G.P.).

The quality of the included studies was evaluated according to their risk of bias assessment based on a recently developed tool.[9] Studies were considered to be of low quality if they had at least a serious risk of bias and to be of high or acceptable quality if their risk of bias was low or moderate, respectively.

STUDIES AND PATIENT CHARACTERISTICS

The literature search initially identified 972 papers; of those, 25 fulfilled the inclusion and exclusion criteria for this review[10-34] (Supporting Fig. S1). The main characteristics of the included studies and patients are presented in Tables 1 and 2.

In total, 2332 (each study contribution from 11 to 401) patients were included in the 25 studies. All but one were cohort studies (three prospective,[21,22,34] one retrospective-prospective,[26] and 20 retrospective[10,12-20,23-25,27-33], while one was a randomized

study comparing the effects of 12 versus 24 months of additional therapy after response to lamivudine in HBeAg-negative CHB.[11] One study was found to have high quality,[11] 14 to have acceptable quality,[10-13,17,22-26,29-32,34] and 10 to have low quality[14-16,18-21,27,28,33] based on their risk of bias assessments (Supporting Table S1).

Eight studies included only HBeAg-positive,[12-16,20,23,31] 11 only HBeAg-negative,[10,11,17,19,21,22,24-26,30,34] and six both HBeAg-positive and HBeAg-negative[18,27-29,32,33] patients. There were 1217 (52.2%) HBeAg-positive and 1115 (47.8%) HBeAg-negative patients. Cirrhosis at baseline was present in 247 (16.1%) of 1532 patients with reported histological severity.

Of the 2332 patients, 1726 (74.0%) discontinued NAs as most, but not all, studies included only patients who discontinued NA therapy (Table 1). Of the 1726 patients who discontinued NAs, 1716 (99.4%) cases were in VR at treatment discontinuation and represented the main patient population of this systematic review. Among them, there were 733 (42.7%) HBeAg-positive and 967 (56.4%) HBeAg-negative patients, while HBeAg status was not clarified in 16 (0.9%) cases. Cirrhosis at baseline was present in 243 (17.8%) of the 1362 patients with reported histological severity who discontinued NAs.

The majority of studies included patients from East Asia,[10-20,22-27,29,31-34] two studies included Caucasian patients,[21,28] and one study had a mixed patient population.[30] The majority of patients in all studies were males. There were wide variations in the patients' baseline parameters such as age as well as serum alanine aminotransferase (ALT) and HBV DNA levels (Table 1). The NAs used were lamivudine in 10,[10-15,17,19,27,32] adefovir in three,[18,21,22] entecavir in three,[26,28,34] telbivudine in one,[16] and several agents in the remaining eight[20,23-25,29-31,33] studies.

There was great heterogeneity among the 25 studies in terms of treatment duration, duration of VR before NA discontinuation, duration of HBeAg seroconversion before NA discontinuation in initially HBeAg-positive patients, and duration of follow-up after NA discontinuation (Table 2). In particular, the definitions of durable VR after NA discontinuation were based on variable serum HBV DNA levels linked to the sensitivities of the assays used in each study, which ranged from 60 to 20,000 IU/mL (or 100,000 cp/mL). VR was based on HBV DNA levels <200 IU/mL (or 1000 cp/mL) in seven,[10,16,19,20,23,27,29] <2000 IU/mL (or 10,000 cp/mL) in 15,[12-14,17,21,22,24-26,28,30-34] and <20,000 IU/mL (or 100,000 cp/mL) in three[11,15,18] studies. The mean duration of VR before NA discontinuation was <12 months in three,[10,15,23] 12-24 months in 13,[12,16-20,22,25,26,29,31,33,34] and >24 months in six[13,21,24,27,28,30] studies, while it was 12 or 24 months in one,[11] 21 or 33 months in one,[14] and 10 or 14 months in another[32] study. The duration of consolidation therapy after HBeAg seroconversion was <12 months in three,[12,15,23] ≥12 months in 10,[13,16,18,20,27-29,31-33] and 0 or 16 months in one[14] of the studies including initially HBeAg-positive patients (Table 2). Patients who restarted treatment within 12 months after NA discontinuation were considered as patients without durable VR.

Biochemical remission (BR) after NA discontinuation was defined as ALT below the upper limit of normal (ULN) in 14,[10,15-18,21-24,27,28,31,33,34] <1.25 × ULN in one,[30] and <2 × ULN in six[11-13,20,25,26] studies, while it was not specified in the remaining four studies.[14,19,29,32]

STATISTICAL ANALYSIS

The probabilities of VR at 6, 12, 24, and 36 months after NA discontinuation were defined as the primary outcomes. Corresponding probabilities were extracted from the survival curves or other relevant information provided in the original papers. To stabilize the variance, all extracted probabilities (p_{ij}) were transformed to logits using the equation $lp_{ij} = \log[p_{ij}/(1 - p_{ij})]$ with the corresponding variance being $1/[N_i \times p_{ij} \times (1 - p_{ij})]$, where p_{ij} represents the estimated probability from the ith study at the jth time point and N_i represents the corresponding reference population at baseline. It is highly likely that the number at risk does not remain constant across the different time points (i.e., 6, 12, 24, and 36 months after treatment discontinuation). Although some simplistic methods to adjust for differences in the number at risk have been proposed,[35] we used the unadjusted number of patients at baseline N_i to calculate the variance as the required adjustment information was not available in the majority of the original papers.

To calculate pooled logit estimates and corresponding 95% confidence intervals (CIs), the inverse variance method was applied, analyzing each time point separately (univariate method). Therefore, for each time point, only studies that contributed data to that time point were included. However, within each study, probabilities at different time points are expected to be highly correlated. To adjust for that, we further applied

TABLE 3. Data on Off-Therapy Durable VR and BR as Well as on HBsAg Loss in Studies Including CHB Patients Who Discontinued NAs While on VR

	Durable VR (n/N)*			Durable BR (n/N)			HBsAg Loss (n/N)		
Reference	All Patients	HBeAg$^+$	HBeAg$^-$	All Patients	HBeAg$^+$	HBeAg$^-$	All Patients	HBeAg$^+$	HBeAg$^-$
Fung et al.[10]	15/27	—	15/27	20/27	—	20/27	NR	—	NR
Enomoto et al.[11]	5/16	—	5/16	5/16	—	5/16	NR	—	NR
Yeh et al.[12]	52/71	52/71	—	52/71	52/71	—	0/71	0/71	—
Fung et al.[13]	8/22	8/22	—	15/22	15/22	—	NR	NR	—
Wang et al.[14]	87/125	87/125	—	NR	NR	—	NR	NR	—
Kuo et al.[15]	42/124	42/124	—	42/124	42/124	—	MR	NR	—
Cai et al.[16]	4/7	4/7	—	7/7	7/7	—	NR	NR	—
Liu et al.[17]	30/61	—	30/61	33/61	—	33/61	8/61	—	8/61
Jung et al.[18]	13/19	7/10	6/9	15/19	NR	NR	0/19	0/10	0/9
Chan et al.[19]	16/53	—	16/53	NR	—	NR	9/53	—	9/53
Chaung et al.[20]	4/39	4/39	—	24/39	24/39	—	0/39	0/39	—
Hadziyannis et al.[21]	18/33	—	18/33	18/33	—	18/33	14/33	—	14/33
Ha et al.[22]	50/145	—	50/145	52/145	—	52/145	NR	—	NR
Song et al.[23]	28/48	28/48	—	NR	NR	—	NR	NR	—
He et al.[24]	47/66	—	47/66	NR	—	NR	2/66	—	2/66
Kim et al.[25]	12/45	—	12/45	21/45	—	21/45	NR	—	NR
Jeng et al.[26]	40/95	—	40/95	52/95	—	52/95	0/95	—	0/95
Kwon et al.[27]	12/16	NR	NR	12/16	NR	NR	2/16	NR	NR
Ridruejo et al.[28]	26/35	24/33	2/2	NR	NR	NR	18/35	NR	NR
Sohn et al.[29]	16/95	6/41	10/54	NR	NR	NR	0/95	0/41	0/54
Patwardhan et al.[30]	12/33	—	12/33	17/33	—	17/33	0/33	—	0/33
He et al.[31]	89/97	89/97	—	96/97	96/97	—	11/97	11/97	—
Chen et al.[32]	63/188	30/83	33/105	NR	NR	NR	23/185	6/83	17/105
Jiang et al.[33]	25/72	11/33	14/39	42/72	14/33	28/39	NR	NR	NR
Seto et al.[34]	15/184	—	15/184	142/184	—	142/184	0/184	—	0/184

*n/N, number of patients with response/number of patients in VR at discontinuation of NAs.
Abbreviation: NR, not reported.

the multivariate meta-analysis method, which analyzes all outcomes simultaneously. For each study, the correlation between outcomes at different time points was calculated using the method proposed by Barrett et al.[36] Results from multivariate analysis were very similar to those obtained from univariate analysis, especially for the probabilities of VR at 6 and 12 months after NA discontinuation as nearly all studies provided data for these time points. Pooled logit estimates and their CIs were back-transformed to probabilities by the inverse logit transformation: $p_{ij} = e^{lpij}/(e^{lpij} + 1)$, where e is the base of the natural logarithm.

To determine whether study-level factors influenced the probability of VR at 12 months after NA discontinuation, which represented the minimum posttherapy follow-up, univariate meta-regression models were carried out. Subgroup analyses, analyzing separately HBeAg-positive and HBeAg-negative patients, were carried out, whereas results from the two subgroups were compared using the multivariate Wald test. Logistic random effects regression models were used to pool the overall probability of VR, BR, and HBsAg loss. Information on the timing of BR and HBsAg loss was not available in the majority of the papers. All analyses were performed using the commands metan, mvmeta, and metareg in STATA (version 13.0; Stata Corp, College Station, TX).

Results

DURABLE OFF-NA VR AND BR

Regardless of the duration of follow-up, durable VR after NA discontinuation was reported in 729 of the 1716 patients (Table 3) (random effects pooled estimate = 45.8%, 95% CI 35.5-56.5; P for heterogeneity < 0.001). The overall pooled rate of durable VR was numerically higher in patients who were HBeAg-positive (392/733; random effects = 50.6%, 95% CI 34.4-66.7; P for heterogeneity < 0.001) than HBeAg-negative patients before NAs (325/967; random effects = 38.0%, 95% CI 28.7-48.3; P for heterogeneity < 0.001).

Taking into consideration the duration of follow-up, the pooled rates (95% CI) of VR were 68.2%

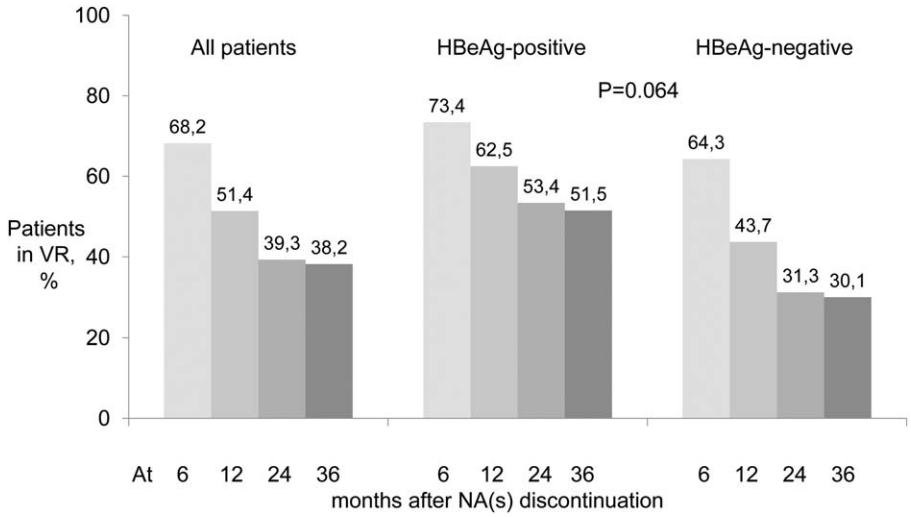

FIG. 1. Rates of off-therapy VR in CHB patients who discontinued NAs in VR.

(60.2-75.2), 51.4% (41.4-61.4), 39.3% (27.9-52.1), and 38.2% (26.6-51.2) at 6, 12, 24, and 36 months, respectively, after NA discontinuation. The 6-month, 12-month, 24-month, and 36-month pooled rates (95% CI) of VR were numerically higher in initially HBeAg-positive patients (73.4% [60.6-83.2], 62.5%

TABLE 4. Factors That May Potentially Affect or Can Be Associated With the Rates of Durable VR at 12 Months After Discontinuation of NAs: Random Effects Models Were Used for the Estimation of Corresponding Probabilities

	Probability of Durable VR, % (95% CI)	Odds Ratio (95% CI)	*P*
All patients			
VR defined by HBV DNA			0.180
<200 IU/mL	34.1 (17.4-56.0)	1	
<2000 IU/mL	54.7 (41.9-66.8)	2.33 (0.83-6.57)	
<20,000 IU/mL	62.0 (38.3-80.9)	3.14 (0.84-11.71)	
Duration of on-NAs VR			0.616
<12 months	52.5 (28.1-75.8)	1	
12-24 months	48.1 (34.9-61.5)	0.84 (0.26-2.71)	
>24 months	61.1 (39.0-79.4)	1.42 (0.36-5.62)	
HBeAg-positive patients			
VR defined by HBV DNA			0.289
<200 IU/mL	42.0 (16.6-72.4)	1	
<2000 IU/mL	71.2 (52.2-84.8)	3.41 (0.74-15.71)	
<20,000 IU/mL	63.1 (32.8-85.7)	2.37 (0.39-14.33)	
Duration of on-NA VR			0.544
<12 months	53.2 (27.4-77.4)	1	
12-24 months	72.0 (49.2-87.2)	2.26 (0.52-9.84)	
>24 months	60.3 (27.1-86.1)	1.33 (0.22-7.98)	
Duration of consolidation therapy after HBeAg seroconversion			0.928
<12 months	62.6 (38.5-81.8)	1	
≥12 months	64.1 (42.2-81.3)	1.06 (0.28-4.02)	
HBeAg-negative patients			
VR defined by HBV DNA			0.513
<200 IU/mL	29.3 (10.8-58.7)	1	
<2000 IU/mL	48.0 (30.6-65.9)	2.24 (0.53-9.41)	
<20,000 IU/mL	51.4 (15.4-86.1)	2.56 (0.30-22.03)	
Duration of on-NA VR			0.017
<12 months	50.0 (14.9-85.1)	1	
12-24 months	34.1 (22.8-47.6)	0.52 (0.08-3.24)	
>24 months	75.0 (50.5-89.8)	3.00 (0.39-23.30)	

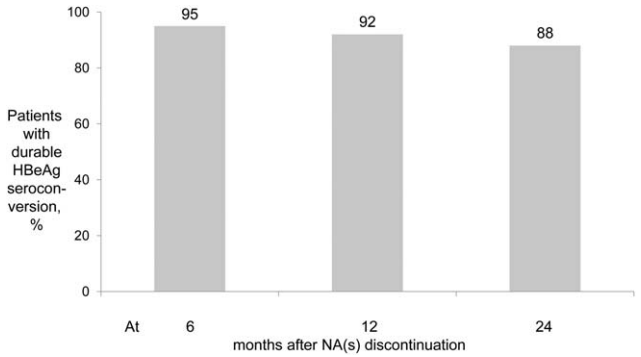

FIG. 2. Rates of durable HBeAg seroconversion in initially HBeAg-positive patients who discontinued NAs after achieving on-therapy HBeAg seroconversion and HBV DNA undetectability. All patients received at least 6 months of consolidation therapy.

[47.8-75.3], 53.4% [34.6-71.3], 51.5% [31.9-70.6]) than HBeAg-negative patients (64.3% [50.7-76.0], 43.7% [30.5-57.9], 31.3% [18.6-47.7], 30.1% [17.8-46.1]) ($P = 0.064$) (Fig. 1). The forest plots of the probabilities of durable VR at 12 months after NAs discontinuation in all, initially HBeAg-positive, and HBeAg-negative patients are presented in Supporting Fig. S2A-C.

The pooled rates of durable VR were numerically lower in studies defining VR by HBV DNA <200 than < 2000 or < 20,000 IU/mL ($P = 0.180$) (Table 4) or by HBV DNA <200 versus < 2000-20,000 IU/mL (VR [95% CI] at 12 months after NA discontinuation: 34.1% [17.6-55.7] versus 56.3% [45.2-66.8]; odds ratio = 2.49, 95% CI 0.92-6.72, $P = 0.073$). Similarly, the pooled rates of durable VR were not significantly different according to the VR definition in either initially HBeAg-positive ($P = 0.289$) or HBeAg-negative ($P = 0.513$) patients.

The pooled probability (95% CI) of durable VR at 12 months after NA discontinuation (or any other time point) did not differ between high-quality/acceptable and low-quality studies in all patients (50.8% [38.2-63.4] versus 53.7% [35.4-71.1], $P = 0.802$), HBeAg-positive patients (63.9% [43.8-80.0] versus 62.0% [35.0-83.8], $P = 0.938$), or HBeAg-negative patients (43.4% [28.3-59.7] versus 46.0% [15.2-80.2], $P = 0.900$).

In studies with initially HBeAg-positive patients, the durability of HBeAg seroconversion following NA discontinuation was also evaluated. In six studies with 289 HBeAg-positive patients providing such data,[12,13,18,23,29,31] the pooled probability (95% CI) of durable HBeAg seroconversion was 95.4% (91.9-97.4), 91.9% (88.1-94.6), and 88.0% (80.2-93.0) at 6, 12, and 24 months after NA discontinuation, respectively, without significant heterogeneity among the studies (Fig. 2).

Durable BR after NA discontinuation was observed in 676 of 1106 patients with available data (random effects pooled estimate = 65.4%, 95% CI 53.8-75.4; P for heterogeneity < 0.001) (Table 3; Supporting Fig. S3A). The rate of durable BR was numerically, but not significantly, higher in initially HBeAg-positive patients (268/403; random effects = 76.2%, 95% CI 51.8-90.5; P for heterogeneity < 0.001) than HBeAg-negative patients (394/687; random effects = 56.7%, 95% CI 47.4-65.6; heterogeneity, $P < 0.001$) ($P = 0.130$) (Supporting Fig. S3B,C). In 17 studies providing such data,[10-15,17,18,20-22,24,26,29-31,34] treatment was restarted in 568 (96%) of 594 patients without durable BR or 568 (79%) of 721 patients without durable VR.

HBSAG LOSS

HBsAg loss was observed in 87 of 1085 patients (random effects pooled estimate = 2.0%, 95% CI 0.3-10.6; P for heterogeneity < 0.001) without significant difference between initially HBeAg-positive patients (17/341; random effects = 1.0%, 95% CI 0.5-15.2; P for heterogeneity < 0.001) and HBeAg-negative patients (50/693; random effects = 1.7%, 95% CI 0.2-13.3; P for heterogeneity < 0.001) (Table 3). HBsAg loss was achieved during NA therapy in most cases and maintained after NA discontinuation in all cases.

FACTORS ASSOCIATED WITH DURABLE OFF-NA VR

The duration of on-therapy VR did not affect the probability of durable VR in all or in initially HBeAg-positive patients, but it was found to have a strong effect in HBeAg-negative patients (Table 4). In particular, the VR rates at 12 months after NA discontinuation in HBeAg-negative patients were 35.6% (95% CI 24.6-48.2) in studies with duration of on-therapy VR ≤ 24 months and 75.0% (95% CI 51.1-89.6) in studies with duration of on-therapy VR > 24 months (odds ratio = 5.45, 95% CI 1.68-17.70; $P = 0.005$). The duration of on-therapy VR was not found to affect the durable BR rates in all, HBeAg-positive, or HBeAg-negative patients (data not shown).

The probability of durable HBeAg seroconversion at 12 months after NA discontinuation (or any other

time point) was not different in studies with mean duration of consolidation therapy after HBeAg seroconversion <12 or ≥12 months (93.0, 95% CI 86.8-96.4, versus 91.2, 95% CI 85.9-94.7; $P = 0.588$). It should be noted, however, that there were only two studies with duration of consolidation therapy <12 months, in which consolidation therapy was given for 6-12 months.[12,23] The mean duration of consolidation therapy (<12 or ≥12 months) was also found not to affect the durable VR rates following NA discontinuation (Table 4).

Variable additional predictors of durable off-NA VR were reported in the included studies, often providing conflicting results. In particular, off-NA VR was reported to be associated with lower baseline ALT in one,[30] low baseline HBV DNA (<200,000 IU/mL) in one,[26] and absence of baseline cirrhosis in another study with HBeAg-negative patients[25] but not in any other study included in this review. In addition, younger age was associated with off-NA VR in three studies (two with HBeAg-negative and one with both HBeAg-positive and HBeAg-negative patients),[17,22,32] whereas female gender was associated with off-NA VR in the HBeAg-negative patients of one study.[32] The probability of off-NA VR was not affected by HBV genotype (mainly genotypes B and C) in 10 studies reporting such data.[12-15,19,24,26,29,31,32] The probability of off-NA VR was not associated with the type of NA in five studies using high (entecavir or tenofovir) and low genetic barrier NAs (lamivudine, adefovir, telbivudine) including 336 patients (138 HBeAg-positive, 198 HBeAg-negative),[24,25,30,31] while it was higher in 95 entecavir-treated than 52 lamivudine-treated or telbivudine-treated patients with HBeAg-negative CHB in one study.[25] Lower HBsAg levels at the end of NA therapy were associated with off-NA VR in three studies (one with HBeAg-positive, one with HBeAg-negative, one with both HBeAg-positive and HBeAg-negative patients)[15,16,19,27] and in the HBeAg-negative patients of another study[32] including a total of 298 patients but not in three studies with HBeAg-negative patients[21,26,34] and in the HBeAg-positive patients of another study[32] including a total of 402 patients. HBsAg levels at the end of NA therapy were associated with HBsAg loss in two studies with HBeAg-negative patients,[19,21] while HBsAg kinetics, but not HBsAg levels, were associated with off-NA VR in one study with HBeAg-positive patients.[16]

In the studies with initially HBeAg-positive patients, the probability of durable HBeAg seroconversion following NA discontinuation was found to be associated with the patients' age in three studies including 256 patients[14,23,32] but not in seven studies including 463 patients.[12,13,15,18,28,29,31] Moreover, the probability of durable HBeAg seroconversion following NA discontinuation was found to be associated with the timing of HBeAg seroconversion in three studies including 73 patients[10,27,28] but not in five studies including 489 patients.[14,15,23,29,31]

CLINICAL EVENTS IN PATIENTS WITH CIRRHOSIS AT BASELINE

Biochemical relapse following NA discontinuation was reported in 28 (39%) of 72 patients with baseline cirrhosis in three studies providing such data.[12,15,26] Liver decompensation developed in two (0.8%) of 243 patients with baseline cirrhosis,[10-12,14,15,18,19,25-34] while jaundice developed in another six (2.5%) patients.[15] Retreatment was reported to be effective in all but one patient with cirrhosis who died because of liver failure.[15]

Discussion

The safety of NA discontinuation remains one of the most controversial topics in the management of CHB patients.[37,38] Scientific guidelines from Europe and the United States recommend that NA therapy should continue until HBsAg loss, at least in patients with HBeAg-negative CHB.[1,2] However, some groups have started exploring the safety of NA discontinuation in both HBeAg-positive and HBeAg-negative CHB Caucasian patients who remain positive for HBsAg. In addition, there is an increasing number of studies from Asia where the guidelines recommend NAs to be discontinued rather early mainly due to the accumulating economic burden from long-term therapy in limited-resource countries with high HBV prevalence.[39]

We identified 25 studies published from 2002 to 2014 which included more than 1700 patients in whom NAs were discontinued. Given that there has been no consensus on the criteria for NA discontinuation, posttreatment follow-up, definition of relapse, indications for retreatment, and other critical factors, there was great heterogeneity among the studies (Tables 1 and 2), probably reflecting the local guidelines and clinical practice as well as the treating physicians' attitudes on this topic. Of the patients who were in VR at NA discontinuation defined by undetectable serum HBV DNA and negative HBeAg, the pooled

overall rate of durable VR was approximately 46%, with most of the relapses occurring within the first or second year after NA discontinuation. In particular, the pooled durable VR rates were 68% at 6, 51% at 12, 39% at 24, and 38% at 36 months after NA discontinuation, being higher in initially HBeAg-positive patients (12 months: 63%, 24 months: 53%) than HBeAg-negative patients (12 months: 44%, 24 months: 31%) ($P = 0.064$).

The overall rates of durable BR following NA discontinuation were approximately 20% higher compared to those of durable VR in all (65% versus 46%), HBeAg-positive (76% versus 51%), and HBeAg-negative (58% versus 38%) patients. Such differences may depend on the definitions of BR and VR but were consistent among studies, suggesting that virological relapses are not always of clinical relevance, particularly when they are based on low viremia levels. According to our findings, no significant differences in durable VR rates were observed between studies defining VR by HBV DNA <200 IU/mL and <2000-20,000 IU/mL, but durable VR rates were at least 20% lower in the former type of study in all (34% versus 55%-62%), HBeAg-positive (43% versus 62-71%), and HBeAg-negative (29% versus 48%-51%) patients (Table 4). Given that immunological remission after the end of therapy represents a desirable and attainable therapeutic target, maintenance of the inactive carrier state seems to be the most clinically relevant endpoint for patients discontinuing NAs. Therefore, HBV DNA levels <2000 IU/mL or < 10,000 cp/mL accompanied by normal ALT activity instead of undetectable HBV DNA by sensitive assays seem to represent a reasonable definition of posttherapy remission regardless of type of therapy.[1] Such a conservative definition of post-NA remission, however, may lead to unnecessary early retreatment in some, particularly HBeAg-negative, patients, who often develop early transient beneficial flares that can lead to long-lasting remission and even spontaneous HBsAg clearance.[21,40] Thus, definitions of relapse based on just one or two HBV DNA determinations usually underestimate the clinically relevant long-term VR rate in this setting. Therefore, close follow-up at least during the first 12 months following NA cessation and confirmation of relapses taking into consideration the ALT and HBV DNA kinetics instead of single levels should be the preferred management of such patients before retreatment is considered.

A critical factor associated with the probability of durable VR in HBeAg-negative patients was the duration of on-therapy VR. Our results suggest that the pooled probability of durable VR is significantly increased (12 months: 36% versus 75%) in patients who remain in VR under NAs for more than 24 months. Such a finding does not support the existing guidelines from the Asian-Pacific Association for the Study of the Liver, which recommend NAs to be discontinued in HBeAg-negative CHB patients who remain in VR for only 18 months.[39]

In initially HBeAg-positive patients, the probability of durable VR was not found to be significantly associated with the duration of on-therapy VR. The probability of durable HBeAg seroconversion was relatively high starting from 95% at 6 months and decreasing only to 92% and 88% at 12 and 24 months, respectively, after NA discontinuation. The probability of durable HBeAg seroconversion was also not found to be associated with the duration of on-therapy VR or of consolidation therapy. Such satisfactory response rates, particularly for durable HBeAg seroconversion, were achieved in HBeAg-positive CHB patients with on-NA HBeAg seroconversion and HBV DNA undetectability followed by >6 months consolidation therapy in all studies (all but two > 12 months). Thus, although it may initially seem to be controversial, these findings further support the validity of the existing guidelines recommending a minimum of 6-12 months of consolidation therapy in HBeAg-positive patients who achieve seroconversion to antibody to HBeAg.[1,2,39] Because NAs were discontinued after consolidation therapy following HBeAg seroconversion, additional potential benefit from long (>24 months) duration of on-therapy VR could not be evaluated as such on-therapy VR was reported in only one study.[13]

HBsAg loss, which represents the treatment endpoint that is closest to clinical HBV cure,[1,2] was reported to occur in a minority of cases (2% by random effects model). In fact, the reported rate probably overestimates the overall probability of HBsAg loss in NA-treated patients as only patients with a complete on-therapy VR were included in these studies. On the other hand, the probability of HBsAg loss following NA discontinuation may be affected by the definition of post-NA remission and particularly the indications for retreatment as early reinstitution of NA therapy may prevent the development and evolution of transient beneficial flares that have been shown to precede HBsAg clearance in most cases.[21,40]

The identification of predictors of durable VR after NA discontinuation is of great importance. However, despite several attempts to identify predictors of durable VR at the time of NA discontinuation, no clear predictor of durable VR or BR can be reliably

identified from the existing studies, which may be related to the heterogeneity of studies, variation in the definitions of VR, and evaluation of inconsistent potential predictors among most studies. In fact, the predictability of all potential predictors reported by some studies has not been confirmed in subsequent and usually larger studies. The type of NA was not found to be associated with the probability of off-NA remission in five of six studies providing such data. However, only a few studies have compared low and high genetic barrier NAs for posttherapy responses, while high genetic barrier NAs have been represented mainly by entecavir as tenofovir has only recently been introduced in many eastern Asian countries, where most of the included studies have been performed.

The data on the safety of NA discontinuation in patients with preexisting cirrhosis are limited. There have been a few Asian studies reporting successful NA discontinuation in patients with baseline cirrhosis, but such a strategy cannot be recommended in this setting because at least a few cases of life-threatening relapse, including one patient's death, have been reported in these studies.[15,26]

In conclusion, discontinuation of long-term NA therapy may be attempted if close follow-up can be guaranteed in patients without advanced liver disease. As also stated in the recent World Health Organization guidelines,[41] NA discontinuation may be considered not only in HBeAg-positive patients without cirrhosis who achieve stable HBeAg seroconversion for at least 12 months but also in HBeAg-negative patients without cirrhosis who remain in BR and VR under NAs for a few years. The optimal duration of on-therapy HBV DNA undetectability before NA discontinuation in HBeAg-negative patients is currently unknown, but it should be >24 months. Post-NA virological and biochemical relapses will occur in a proportion of patients, most frequently within the first or second year. However, no detrimental effect has been reported in such patients without cirrhosis, and retreatment can always reintroduce VR. Additional studies are required to identify predictors of durable VR, but no strong conclusion will be drawn before uniform and well-accepted definitions of post-NA relapse and criteria for retreatment are agreed and used.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.28438/suppinfo.