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Is it possible to stop nucleos(t)ide analogue treatment in chronic hepatitis B patients?

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Abstract

Chronic hepatitis B (CHB) remains a challenging global health problem, with nearly one million related deaths per year. Nucleos(t)ide analogue (NA) treatment suppresses viral replication but does not provide complete cure of the hepatitis B virus (HBV) infection. The accepted endpoint for therapy is the loss of hepatitis B surface antigen (HBsAg), but this is hardly ever achieved. Therefore, indefinite treatment is usually required. Many different studies have evaluated NA therapy discontinuation after several years of NA treatment and before HBsAg loss. The results have indicated that the majority of patients can remain off therapy, with some even reaching HBsAg seroconversion. Fortunately, this strategy has proved to be safe, but it is essential to consider the risk of liver damage and other comorbidities and to ensure a

close follow-up of the candidates before considering this strategy. Unanswered questions remain, namely in which patients could this strategy be effective and what is the optimal time point at which to perform it. To solve this enigma, we should keep in mind that the outcome will ultimately depend on the equilibrium between HBV and the host's immune system. Viral parameters that have been described as good predictors of response in HBeAg(+) cases, have proven useless in HBeAg(-) ones. Since antiviral immunity plays an essential role in the control of HBV infection, we sought to review and explain potential immunological biomarkers to predict safe NA discontinuation in both groups.

Key words: CD8; Lamivudine; Nucleos(t)ide analogues; Tenofovir; Chronic hepatitis B; Entecavir; Hepatitis B virus; Treatment cessation

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Core tip: Nucleos(t)ide analogue (NA) treatment efficiently suppress hepatitis B virus replication. However, hepatitis B surface antigen loss, the optimal endpoint of NA therapy, is rarely achieved. Thus, a major unmet need in the management of chronic hepatitis B is the definition of earlier and safe treatment stopping points. There is growing clinical evidence that the majority of patients can benefit from this strategy after long-term NA therapy; yet, no criteria that distinguish which cases can safely stop treatment is established. We review here different biomarkers that could serve as a prognostic tool to safely discontinue therapy, focusing on host antiviral immunity.

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INTRODUCTION

According to recent data from the World Health Organization, about 257 million people suffer from chronic hepatitis B (CHB) worldwide. Hepatitis B virus (HBV) infection remains a major global health concern, as the disease itself and its complications, mainly hepatocellular carcinoma (HCC) and cirrhosis, caused 887000 deaths in 2015 alone. The estimated worldwide incidence of HCC in 2012 was 782000 cases, representing the fifth and the ninth most common cancer in males and females respectively. Moreover, HCC was the second cause of global cancer mortality, as it tends to have very poor prognosis with an overall ratio of mortality to incidence of 0.95^[1].

Although the actual HBV vaccine is 95% effective,

vaccination coverage is still suboptimal in many highly endemic areas. Besides, most of the current HBV-infected persons were born before the vaccine was widely accessible^[2-4]. HBV infection chronification is not fully understood. The HBV genome assembly into a stable mini-chromosome, known as covalently closed circular (ccc)DNA, which can integrate into and persist in the hepatic cell nucleus. In addition, the immune response against HBV is profoundly impaired^[5,6]. Both are, in fact, the main reasons why indefinite treatment is usually necessary.

Immune modulators were the first approach to CHB treatment. The first one, interferon (IFN)- α was approved in 1991, being afterwards substituted by its pegylated form (Peg-IFN- α) as the latter provides a safer profile. The principal mechanism of Peg-IFN- α therapy relies on the induction of long-term immune control, which occurs in almost half of the responders and with limited treatment duration. However, it poses significant drawbacks, including an adverse safety profile and a high response variableness, the reasons why a number of patients are ineligible, unsuitable or reluctant to partake in this treatment alternative^[7,8].

At present, nucleos(t)ide analogues (NAs) constitute the lynchpin of CHB therapy, as they facilitate achievement of viral suppression in almost all adherent patients, while having an overall favourable safety profile^[7-9]. The currently approved NAs for CHB treatment in the United States and Europe include lamivudine (LMV), telbivudine (TBV), adefovir dipivoxil (ADV), tenofovir (disoproxil fumarate, TDF; alafenamide, TAF) and entecavir (ETV). The NA mechanism of action comprises viral polymerase inhibition, which leads to decreased virion assembly and ultimately a hypothetical cccDNA downturn that would only be appreciated after an extended period of treatment^[10,11].

Nonetheless, NAs are not able to stop *de novo* cccDNA synthesis in recently infected hepatocytes; thus, lingering viremia could perpetuate the viral repository. That is the reason why "complete cure" is not a realistic endpoint of NAs to date. "Functional cure", understood as HBV DNA and hepatitis B surface antigen (HBsAg) seroclearance with or without seroconversion, constitutes a more plausible goal. However, it is achieved only in a small proportion of the treated patients. Lifelong NA therapy is usually necessary, especially in hepatitis B e antigen-negative [HBeAg(-)] cases^[7,12,13].

Since indefinite treatment is mandatory, development of viral resistance is a paramount concern, especially with the first- and second-generation oral NAs such as LMV, TBV and ADV. Fortunately, that problem seems to have been overcome by the new agents TDF/TAF and ETV, as they present low resistance rates and high efficacy with a very favourable safety profile^[14,15].

Combination therapy has also been proposed as a strategy for HVB eradication, but results are still under evaluation and intense debate. Its rationale

comprises attacking the virus in different parts of its life cycle, and follows practical successes observed in other infectious diseases, like hepatitis C virus and human immunodeficiency virus. Potential objectives regarding this approach include viral targeting (viral entry, cccDNA, RNA interference, encapsidation, DNA replication, *etc*) as well as innate and adaptive immunomodulation (IFN, Toll-like receptor/RIG-1 agonists; and checkpoint inhibitors, T cell modification and vaccination respectively).

Other trials that have evaluated the synergies between innate immunity potentiation and NAs have already shown promising results. A preclinical phase study that combined a woodchuck hepatitis virus DNA vaccine, a programmed cell death protein 1 (PD-1) inhibitor and ETV showed restoration of the cytolytic capacities of HBV-specific T cells and better control of viral replication. Another study that associated a DNA vaccine with any NA revealed no differences in relapse after NA cessation. A third study that blended an HBsAg vaccine with LMV did not find clinical differences^[16-19].

If theoretically attractive, current guidelines do not recommend combination therapy for clinical practice^[9,20]. The ultimate and thus optimal target of HBV therapy for HBeAg(-) and HBeAg(+) patients comprises viral eradication. Such would involve HBsAg seroconversion or seroclearance and cccDNA elimination from hepatocytes^[21]. Unfortunately, it is not a likely outcome, and recommended goals point towards sustained inhibition of replication and maintenance of alanine aminotransferase (ALT) enzyme levels within the normal range^[9,20,22]. Achievement of these objectives has been shown to stop the inflammation cascade and fibrosis progression^[23,24], with a consequent improvement in life-quality and survival^[25]. The weight of the beneficial effects of the latest generation NAs over the risk of HCC are still controversial, as the latter develops even despite therapy^[26-28].

It seems, then, reasonable to bear in mind that any strategy involving NA treatment withdrawal must guarantee the patient's safety and, therefore, the maintenance of the aforementioned objectives.

CLINICAL EVIDENCE REGARDING NA TREATMENT CESSATION

There is a growing body of evidence that helped to elucidate whether NA therapy cessation is safe and effective. A relevant study by Hadziyannis *et al.*^[29] must be pointed out as a point of inflexion regarding the NA cessation approach. It showed a significantly higher HBsAg clearance rate (almost reaching 40%) in the HBeAg(-) CHB patients that stopped after 5 years under ADV therapy, in comparison to that reported for their equals under NA. Since then, a set of investigations have attempted to clarify whether stopping treatment with NA may have an additional benefit in the loss

of HBsAg, showing achievement of rates between 20%-24%^[30,31].

Some parameters have been pointed out as possible predictors of both sustained viral response and HBsAg loss. Among these, it is worth highlighting the decrease of quantitative (q)HBsAg. Other biomarkers that could permit identification of patients in which NA cessation will be safe will be reviewed broader, later on.

The recent FINITE study^[32] was the first randomized controlled trial that compared standard TDF therapy continuation against its interruption in HBeAg(-) patients that had been under treatment for at least 3.5 years. In line with the previous commented work, 13 out of 21 patients in the cessation arm remained off-therapy and 4 of them even achieved HBsAg seroclearance after 3 years of follow-up. No unexpected safety issues were reported. These and the other studies about NA interruption that have been published to date are summarised in Table 1.

Some of the current HBV management guidelines^[9,22] have begun to consider treatment cessation in other selected populations of patients. The most accepted election criteria include cirrhosis absence, treatment for at least 2 or 3 years, sustained viral suppression and guaranteed patient monitoring (Table 2). Concerns regarding treatment cessation include virological and clinical relapse but also the possibility of dangerous complications, such as hepatic decompensation, liver failure and, ultimately, death. Serious complications are uncommon, and some meta-analyses have shown a decompensation rate of less than 1% in patients that presented baseline cirrhosis^[33,34]. Therapy reestablishment proved to be effective in most cases, but also cases of death after liver failure have been reported.

A recent study provided alert to the risk of relapse and potentially fatal effects among Caucasian cirrhotic patients with HBeAg(+) HBV virus infection^[35]. Two patients died of liver-related events: one after decompensation and sepsis, and the other one after developing a multicentric HCC 10 years after the NA treatment cessation. Nevertheless, both of those patients had presented with advanced fibrosis and cirrhosis, respectively, at the time of therapy discontinuation. Furthermore, although a few studies have claimed benefits of long-term treatment regarding HCC incidence, as previously stated, it is not doubtlessly prevented by NA therapy^[26-28,36,37].

Hence, considering that the treatment withdrawal could lead to severe flares and even death in a few cases it should be avoided in patients with advanced fibrosis or cirrhosis, and a close follow-up must always be guaranteed for the rest of the cases^[38]. However, severe complications are rare, and research must continue to address the optimal NA cessation point. The identification of reliable factors capable of predicting clinical, virological and biochemical relapse, or the maintenance of the viral response, would be of vital

Table 1 Summary of relevant NA treatment discontinuation studies

Study	Patients off NA, <i>n</i>				Treatment characteristics				Outcomes			
	Total	HBeAg(+)	HBeAg(-)	Cirrhosis	Age in year	Sex, male	Ethnicity	NA	Treatment duration in mo	Durable virologic response, <i>n</i>	HBsAg loss, <i>n</i>	Deaths, <i>n</i>
Fung <i>et al</i> ^[100] (2004)	27	0	27	7	45	40	Asian	LMV	24	15	NR	0
Enomoto <i>et al</i> ^[101] (2008)	22	0	22	3	49	15	Asian	LMV	NR	5	NR	0
Yeh <i>et al</i> ^[102] (2009)	71	71	0	11	41	55	Asian	LMV	NR	52	0	0
Fung <i>et al</i> ^[103] (2009)	22	22	0	NR	28	16	Asian	LMV	74	8	NR	0
Wang <i>et al</i> ^[104] (2010)	125	125	0	0	26/32	95	Asian	LMV	24-36	87	NR	0
Kuo <i>et al</i> ^[105] (2010)	124	124	0	NR	NR	NR	Asian	LMV	14	42	NR	1
Cai <i>et al</i> ^[106] (2010)	11	11	0	NR	29	12	Asian	TBV	24	4	NR	0
Liu <i>et al</i> ^[107] (2011)	61	0	61	0	32	50	Asian	LMV	27	30	8	0
Jung <i>et al</i> ^[108] (2011)	19	10	9	4	37	12	Asian	ADV	33	13	0	0
Chan <i>et al</i> ^[109] (2011)	53	0	53	18	56	43	Asian	LMV	27	16	9	NR
Chauang <i>et al</i> ^[108] (2012)	39	39	0	NR	34	24	Asian	LMV, ADV, ETV	21	4	0	0
Hadziyannis <i>et al</i> ^[29] (2012)	33	0	33	0	53	38	Caucasian	ADV	56	18	14	0
Ha <i>et al</i> ^[111] (2012)	145	0	145	NR	33	101	Asian	ADV	26	50	NR	0
Song <i>et al</i> ^[109] (2012)	48	48	0	0	42	29	Asian	ETV, CLE	26	28	NR	NR
He <i>et al</i> ^[110] (2013)	66	0	66	0	35	50	Asian	LMV, ADV, ETV, TBV	37	47	2	0
Kim <i>et al</i> ^[111] (2013)	45	0	45	9	45	33	Asian	LMV, ADV, ETV	38	12	NR	NR
Jeng <i>et al</i> ^[141] (2013)	95	0	95	39	52	83	Asian	ETV	24	40	0	0
Kwon <i>et al</i> ^[112] (2013)	16	NR	NR	NR	NR	NR	Asian	LMV	79	12	2	0
Ridruejo <i>et al</i> ^[113] (2014)	35	33	2	0	NR	NR	Caucasian	ETV	42	26	18	NR
Sohn <i>et al</i> ^[114] (2014)	95	41	54	44	47	53	Asian	LMV, ETV, CLE	22	16	0	0
Patwardhan <i>et al</i> (2014)	33	0	33	0	42	24	Mixed	LMV, ADV, ETV, TDF	64	12	0	0
He <i>et al</i> ^[115] (2014)	97	97	0	NR	26	53	Asian	LMV, ADV, ETV, TBV	35	89	11	0
Chen <i>et al</i> ^[31] (2014)	188	83	105	12	38/49	143	Asian	LAM	20-22	63	23	NR
Jiang <i>et al</i> ^[116] (2015)	72	33	39	8	36	53	Asian	LMV, LMV + ADV, ADV, ETV, TBV	33	25	NR	0
Seto <i>et al</i> ^[117] (2015)	184	0	184	34	54	125	Asian	ETV	37	15	0	0
Huang <i>et al</i> ^[118] (2003)	32	0	32	NR	46	29	Asian	LMV	9	14	NR	NR
Marcellin <i>et al</i> ^[119] (2004)	181	0	181	53	40	156	Asian	LMV	12	53	0	0
Lai <i>et al</i> ^[120] (2006) ¹	325/313	0	325/313	16/31	44/44	248/236	Mixed	ETV/ LMV	≥13	124/78	1/1	2 ²
Marcellin <i>et al</i> ^[121] (2009) ³	181/85	0	181/85	0	40/39	156/74	Asian	LMV	12	52/33	0/0	1 ²
Paik <i>et al</i> ^[122] (2010)	50	0	50	15	39	43	Asian	LMV	24	25	NR	0
Liang <i>et al</i> ^[123] (2011)	84	41	43	0	37	56	Asian	LMV, ADV, ETV or LMV + ADV	33	47	5	NR
Jin <i>et al</i> ^[124] (2012)	138	102	36	17	39	82	Asian	LMV	35	116	82	0
Berg <i>et al</i> ^[132] (2017)	21	0	21	0	45	33	Caucasian	TDF	≥ 48	13	4	0
Van Hees <i>et al</i> ^[35] (2018)	62	62	0	11	43	45	Caucasian	LMV, TDF, ETV, LMV + ADV	70	32	6	2
Rivino <i>et al</i> ^[143] (2018) ⁴	21/27	0/0	21/27	0/0	43/51	14/19	Caucasian/ Asian	TDF, LMV	≥ 24/ ≥ 24	4/14	0/0	NR

Virologic response is considered as defined in the original study. ¹Results expressed as ETV/ LMV; ²Deaths not related with treatment discontinuation according to the authors; ³Two follow-up durations in this study, expressed as: Initial (6 mo)/Long-term (36 mo); ⁴Results obtained in two different cohorts, expressed as: cohort 1/cohort 2. ADV: Adefovir; CLE: Clevudin; ETV: Entecavir; HBsAg: Hepatitis B surface antigen; LMV: Lamivudine; NA: Nucleos(t)ide analogue treatment; NR: Not reported; TBV: Telbivudine; TDF: Tenofovir.

Table 2 NA treatment cessation recommendations in the current hepatitis B virus guidelines

Society	HBeAg(+)	HBeAg(-)	Cirrhosis
EASL (2017) ^[9]	HBsAg clearance (safest) HBeAg seroconversion and HBV DNA undetectability with 6-12 mo of ensuing consolidation therapy	HBsAg clearance Selected patients with ≥ 3 yr virological suppression if guaranteed close postNA monitoring for at least 1 yr	Not recommended
AASLD (2016) ^[20]	HBsAg clearance HBeAg seroconversion with at least 12 mo of persistently normal ALT levels and undetectable serum HBV DNA levels (close monitoring for at least 1 yr)	HBsAg clearance	Not recommended
APASL (2016) ^[22]	HBeAg seroconversion with undetectable HBV DNA and persistently normal ALT levels with 1-3 yr of consolidation therapy	HBsAg clearance with antiHBs seroconversion HBsAg loss with at least 12 mo of consolidation period After treatment for at least 2 yr with undetectable HBV DNA documented on 3 separate occasions, 6 mo apart	Could be considered in compensated cirrhosis with careful monitoring

AASLD: American Association for the Study of Liver Diseases; ALT: Alanine aminotransferase; APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the study of the Liver; HBeAg: Hepatitis B e antigen; HBs: Hepatitis B surface protein; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; NA: Nucleos(t)ide analogue treatment.

importance for clinical practice.

WHY SHOULD NA TREATMENT CESSATION BE CONSIDERED?

Once the safety of NA treatment cessation has been addressed, and keeping in mind that severe complications are rare, the vast benefit may be considered. Notwithstanding that NA treatment has an overall positive safety profile in the general population, some issues arise.

Lifelong NA treatment is an unaffordable burden for healthcare systems. That is why a significant advantage of its cessation would be cost reduction^[22,34]. However, increase in the incidence of some chronic conditions, such as metabolic syndrome, diabetes mellitus and renal failure, may limit NA applicability in the future. Furthermore, we are not aware of potential concerns of NA therapy in elder individuals and research must address this subject. There are some other potential concerns about long-term NA therapy^[39]. The most common side effects involve nephrological and bone toxicity, which are associated with TDF, perhaps the most widely used drug. However, the new tenofovir formulation TAF seems to have a better safety profile regarding these points. Other side effects appear to be related to mitochondrion impairment derived from human DNA polymerase function alteration and resulting in bone, renal and neurologic toxicity.

NAs have a relatively benign safety profile for pregnancy, with telbivudine and tenofovir being the most favourable ones, rated B category by the Federal Drug Administration. On the other hand, ETV has shown deleterious effects for the embryo, being rated C category. Nevertheless, there is a lack of informa-

tion about foetal safety in humans, so NA treatment during pregnancy should only be considered if benefits overwhelm risks.

Despite all the above-mentioned issues, NA counts on its excellent safety profile for almost the totality of the patients eligible for this therapy. To sum up, life-long therapy is usually necessary for the majority of CHB patients because the functional cure is rarely achieved. Therefore, identification of biomarkers to safely stop treatment remains an unmet need in the management of the disease.

POTENTIAL BIOMARKERS TO SAFELY STOP NA TREATMENT

Taking into account that CHB outcome relies on equilibrium between the virus and the host, in the next paragraphs it will be explained how different virological and immunological parameters could be considered or not as predictors to safely discontinue NA treatment.

Sex: Female sex was identified as an independent predictor for sustained virological response after NA discontinuation in HBeAg(-) patients^[31].

Age: Older age has been correlated to higher relapse rates^[31,40,41], possibly reflecting the enhanced immune response in younger individuals.

NA treatment duration: A more extended therapy time would mean more time for an exhausted immune system to recover its response efficacy. Logistic regression has revealed that sustained virologic remission is more likely in HBeAg(-) patients after long periods of treatment, at least over 2 years. Nevertheless, this

parameter has not proven to be useful in HBeAg(+) CHB^[33].

ALT: The predictive role of ALT is controverted. Although it was classically accepted that ALT flares were associated with the virologic response after NA treatment cessation^[42], lower ALT baseline levels have been correlated with higher rates of HBsAg loss^[31]. Also, it has recently been demonstrated that patients who do not flare upon treatment withdrawal are those who remain off-therapy^[43]. Given the observed disparities, more research is needed to elucidate the role of ALT as a biomarker.

DNA: Lower baseline HBV DNA titres were reported as associated independently with lower relapse rates^[44], whereas elevated HBV DNA titres and its persistence after NA interruption also seem to be useful for relapse prediction^[45].

Serum qHBsAg: Decrease in serum qHBsAg has been correlated to HBsAg clearance and has been spotlighted as a possible predictor of sustained response and flares after NA withdrawal^[46-48]. The interest in qHBsAg has been limited, however, due to the low level required for consideration of NA cessation (100-700 IU/mL)^[31,49-51], and which is rarely achieved. Taking into account that these qHBsAg levels are not adequately good predictors to safely discontinue NA therapy, because they would only represent a small portion of cases, more research has been performed to improve the prognostic accuracy.

Noncytopathic viruses, such as HBV, have developed evolutionary mechanisms to remain hidden from the immune system, which is an advantage for their persistence. HBV virus is not highly infectious but produces long-lasting disease that allows it to spread the infection over time. The host/HBV relationship is a dynamic process in which the virus tries to decrease its visibility, whereas the host attempts to prevent and eradicate infection with minimal collateral damage to itself^[52].

Several viral markers have been proposed as potential biomarkers for a safe NA discontinuation, and they are discussed below.

Virological parameters

Serum HBV RNA reflects the transcriptional activity of liver cccDNA, and its decline seems to be a good predictor of HBeAg seroconversion^[53]. Nevertheless, it is commonly undetectable in HBeAg(-) cases^[54], making it useless as a biomarker for stoppage of NA treatment in this increasing population. Moreover, improvement of the HBV RNA assay to make it more sensitive and reproducible, as well as studies in bigger cohorts, are essential before considering it as a potential biomarker for monitoring safe discontinuation of NA therapy in HBeAg(+) patients.

Hepatitis B core (HBc) is an inner nucleocapsid surrounding the viral DNA and is the target of specific

T cell response against the virus. AntiHBc is the first antibody to appear after HBV exposure and it represents a classical serological marker for HBV infection^[55]. The role of antiHBc as a predictor of NA discontinuation, however, has not been fully examined, but it was recently reported that baseline antiHBc level is a strong predictor for HBeAg seroconversion during PEG-IFN- α or NA therapy^[56]. Moreover, there was a trend for an inverse association between antiHBc and clinical relapse after long-term ETV treatment cessation in an Asiatic CHB cohort^[57]. AntiHBc, as a predictor, needs to be further assessed and validated in non-Asiatic cohorts, to verify if it could be useful.

HBV core-related antigen (HBcrAg) includes HBcAg, HBeAg and a pre-core protein (p22cr), and its quantification closely correlates with intrahepatic cccDNA level^[58,59]. In HBeAg(+) CHB patients, the dynamics of HBcrAg accurately predict spontaneous HBeAg seroconversion^[60] and the combination of HBsAg together with HBcrAg quantification help to predict safe discontinuation after NA treatment cessation^[61]. However, most of this research has been performed in Japan with first-generation NAs, so further validation with the currently available NAs and different areas of study is lacking.

In summary, some virological markers could be useful predictors of response in HBeAg(+) patients, but improvement of the assays together with further cohort validation is still needed for HBeAg(-) cases. The other side of the balance is the host's immune defence against the virus, presented in the next section.

Immunological parameters

To achieve control of the HBV infection, a functional adaptive immune response, in particular the cellular immune response, is essential; meanwhile, whether and how HBV triggers the components of the innate immune system remain controversial topics. Even though the humoral response is an effective line of defence against reinfection, in the setting of CHB, the virus persists despite high levels of HBV-specific antibodies^[62] due to antigen overload, and only hepatitis B surface antibody is associated with disease resolution.

Primed HBV-specific CD4 T cells are crucial to allow the adequate activation of HBV-specific CD8 T cells by secretion of proinflammatory cytokines, including IFN- α ^[63]. Afterwards, HBV-specific CD8 T cells play a major role in the resolution of spontaneous infection because they can specifically recognise the infected hepatocytes. Moreover, they can clear the virus by inducing apoptosis of the infected cell as well as by proinflammatory cytokine production to eliminate the virus without causing cell death^[64].

CD4- and CD8-specific HBV responses are vigorous, polyclonal and multispecific in acute-resolving cases, whereas are profoundly impaired in chronically infected patients^[6,65-68]. During CHB, HBV-specific T cell responses gradually lose their functionality and are finally deleted^[69]

due to the high and persistent antigen exposure, in order to avoid host-induced tissue damage, in a process called T cell exhaustion. T cell exhaustion is characterised by high and sustained expression of several negative pathways (*i.e.*, PD-1, immunoregulatory cytokines and so on)^[70-75].

The role of HBV-specific CD4 T cell features as a predictor for NA cessation has not been intensely studied. It could be explained mainly by two reasons. First, the frequency of these cells in the chronic setting of the disease is very low^[76]. Second, due to the nature of CD4 responses, *in vitro* stimulation assays are difficult because these cells are only successfully stimulated by professional antigen-presenting cells. Even though a robust HBV-specific CD4 T cell response is observed in acute resolving cases, and they are essential to support HBV-specific CD8 T cells, the difficulty of assessment makes them less useful than HBV-specific CD8 T cells or other surrogates when trying to find an easy and reproducible immunological marker to stop NA therapy safely.

CHB is one of the best models to study CD8 T cell exhaustion. In the different stages of the natural history of HBV infection, there are different virus-host interactions, reflected by different immune features of HBV-specific CD8 T cells. Bearing in mind that several studies have shown that after long-term NA treatment interruption the majority of patients remain with a viral response after long follow-up^[29,32], we could infer that the host's immunity is controlling HBV replication.

After a long-term NA treatment cessation, HBV-specific CD8 T cells could be given a second chance to fight the virus. If these cells have been restored by the reduced viremia that had been induced by the antiviral therapy at that point, these cases would be able to control the infection in a similar way to chronic infection cases. Therefore, patients with viral control are likely to have a good immune response against the virus, whereas cases with virologic rebound may have a dysfunctional response.

Thus, changes in HBV-specific CD8 T cell phenotype may predict acquisition of antiviral control before HBsAg loss. Taking into account the vital role of HBV-specific CD8 T cells during the natural history of the disease, and its in-depth characterisation achieved over the last two decades, it is presumable that those different features according to viral control could give hints to answer one of the most critical questions regarding CHB management: What kind of patients could benefit from NA therapy interruption?

Boni *et al.*^[77] have extensively studied several immune subsets in different groups of chronically infected patients, including those under NA therapy. In the LMV treated patients, they found an initial improvement of HBV-specific T cell effector capacities against different HBV epitopes (HBcAg, HBeAg) after DNA fall^[77], followed by a decline at 6 mo after the treatment has been stopped; this biphasic behaviour is

irrespective of clinical outcome^[78]. It appears that the first-generation NAs lack the potency needed for HBV-specific T cell restoration.

Succeeding experiments in larger cohorts under the first- and second-generation NA therapies demonstrated that HBV-specific CD8 T cell effector abilities were similar between patients after several years of antiviral treatment and acute resolving cases featured by a PD-1+ phenotype^[79] (Figure 1). PD-1 up-regulation arises on HBV-specific T cells following acute and chronic infection. In the setting of acute infection, PD-1 up-regulation is transient, returning to low levels after viral clearance. However, in chronic infection, PD-1 up-regulation is sustained, and the blockade of PD-1/PD-L1 interaction has shown promising results in restoring virus-specific T cell functionality^[80-83]. Therefore, a PD-1+ phenotype could mean both activation before clearance or exhaustion after persistent and high antigenemia.

The most recent work studying HBV-specific T cell response as a biomarker for HBV therapy discontinuation demonstrated that the patients who did not relapse to NA stoppage featured, during NA treatment, an increased frequency of functional PD-1+ HBV-specific T cells directed against nucleocapsid and polymerase HBV proteins^[43] (Figure 1). The PD-1+ expression on functional HBV-specific T cells may reflect an activated, nonexhausted phenotype. Along these lines, patients with functional HBV-specific CD8 T cells, positive for PD-1, may no longer need NA treatment and should be considered for treatment cessation.

However, the current method is complicated to move from bench to bedside because it involves the study of rare populations by multicolour flow cytometry. Hence, the development of an assay to directly quantify PD-1+ HBV-specific CD8 T cells would be of great interest. Even though the final effectors to clear HBV are the HBV-specific CD8 T cells, it is essential to consider the interplay between them and other components of the immune system to fully understand immunity against HBV and their potential as surrogate biomarkers.

The natural enrichment of natural killer (NK) lymphocytes in the human liver underscores their potential importance in the control of hepatotropic viruses, such as HBV^[84]. During CHB, NK cells express an inhibitory phenotype with altered functionality^[85,86] and have predilection for apoptosis of HBV-specific T cells, resulting in HBV-specific T cell deletion after death ligand-death receptor interaction^[87]. Boni *et al.*^[88] showed a low inflammatory profile of NKs after successful NA therapy, similar to healthy controls. In line with the previously commented work, this lower inflammatory status of NKs correlated with a better HBV-specific T cell response^[88] (Figure 1). Moreover, a partial restoration of blood NK cells was shown following long-term ETV, in terms of antiviral cytokine production compared to naïve CHB^[89].

So, why should study of NKs - instead of HBV-

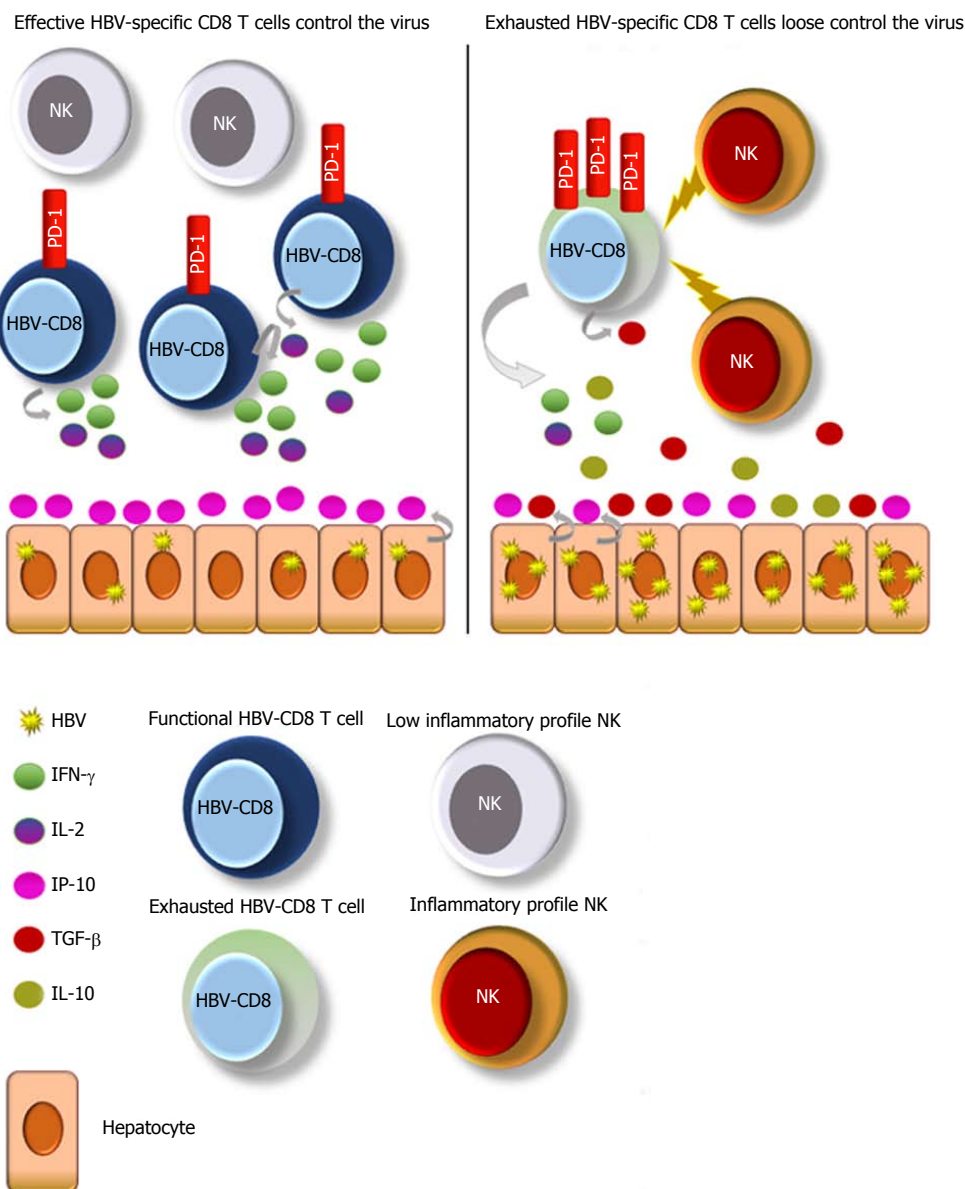


Figure 1 Potential immunological biomarkers for safe nucleos(t)ide analogue discontinuation. A possible strategy to shorten NA therapy would be to check if HBV-specific CD8 T cells have reacquired their antiviral function after long-term therapy. Effective HBV-specific CD8 T cells control the virus: PD-1+ HBV-specific CD8 T cells against different epitopes, able to mount a robust response (IFN- γ , IL-2 production) after antigen encounter, may be a good predictive tool of response. Low inflammatory profile of NK cells may likewise reflect a good point to end therapy. High levels of IP-10 also could point to anti-viral control. Exhausted HBV-specific CD8 T cells lose control of the virus: High and sustained PD-1 expression on HBV-specific CD8 T cells reflects their dysfunctionality. Lower IFN- γ and IL-2 production, along with an immunosuppressive cytokine environment (IL-10, TGF- β), renders these cells to exhaustion. An inflammatory phenotype of NK cells may reflect NK cell-mediated T cell deletion through death receptors. Low levels of IP-10 could dissuade us to stop therapy. HBV: Hepatitis B virus; IP-10: CXCL10; NA: Nucleos(t)ide analogue; NK: Natural killer; PD-1: Programmed cell death protein 1.

specific CD8 T cells - be useful? The study of NK cell inflammation does not involve multimers nor intracellular cytokine staining, as used to assess HBV-specific CD8 T cell responses, resulting in more easily reproducible experiments. A low inflammatory profile of NK cells can be evaluated by surface staining and may reflect an HBV-specific T cell restoration and subsequent control without the need of therapy. Studies in bigger cohorts after stoppage of NA treatment are needed to address if successful NA discontinuation correlates with a lower inflammation phenotype of NK cells.

The third signal of T cell activation requires an

adequate cytokine profile, and long-term NA therapy has been shown to modulate it. Successful viral repression leads to antiviral response stimulation by promoting proinflammatory cytokines such as IFN- γ ^[90,91] and IL-2^[92,93], as well as by decreasing regulatory effectors such as IL-10^[91,94] and TGF- β ^[95]. At least theoretically, the measurement of these cytokines together with HBV-specific T cells or NK cells could also give us clues to establish a good cessation point for therapy (Figure 1).

Not only are the phenotype and functionality of the different immune subsets important components of an adequate milieu during CHB but also the trafficking of

HBV-specific T cells to the infected liver. The migration of lymphocytes to the liver is a complicated process involving adhesion, rolling, triggering and transendothelial migration. Chemokines and their receptors play an essential role in this multistep pathway^[96,97].

After the analysis of several plasma chemokines, the one that appears to be a promising surrogate of HBsAg loss under NA therapy is CXCL10 (IP-10)^[47]. IP-10 is a small protein, secreted by hepatocytes in response to viruses and the subsequent recruitment of proinflammatory CD4 and CD8 T cells to the infected liver^[97] (Figure 1). It was previously reported that baseline serum IP-10 levels were higher in patients with HBsAg loss during NA therapy^[98] and, in line with those findings, another work examined the serum IP-10 kinetics during ETV therapy. Interestingly, they found that IP-10 levels started to significantly increase after the 3rd year of treatment with ETV^[99], which is in line with the timing observed to be necessary to achieve a sustained virological response in the different stopping-treatment studies^[29,32].

It is likely that after a prolonged and effective viral replication suppression under NA treatment, the migration process to the liver is restored and HBV-specific T cells are functional and able to clear the remaining infected hepatocytes, thus reflecting the HBsAg decline.

CONCLUSION

The study of different immune features against HBV, especially HBV-specific CD8 T cells, is a promising strategy to characterise which patients could benefit from NA treatment cessation. Surveying HBV-specific CD8 T cells is complex, as it involves rare population assays. However, different, easier to perform surrogates of this response have been explored recently, providing a more suitable application for clinical use. NA withdrawal is still an active and attractive research field. Nevertheless, even if a considerable number of studies have tried to address this point, their methods have shown marked heterogeneity. Furthermore, although results of some randomised controlled trials are becoming available, more high-quality clinical evidence is needed. It is possible that in the future, therapies able to completely clear cccDNA will be accessible. In the meantime, advantages in the management of CHB may be achieved by using this strategy. Fortunately, the field of immunology shows how basic science can improve the health of our patients.

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