

WJG 20th Anniversary Special Issues (9): Hepatitis B virus**Serum hepatitis B surface antigen levels predict treatment response to nucleos(t)ide analogues**

Chien-Hung Chen, Yi-Chun Chiu, Sheng-Nan Lu, Chuan-Mo Lee, Jing-Houng Wang, Tsung-Hui Hu, Chao-Hung Hung

Chien-Hung Chen, Yi-Chun Chiu, Sheng-Nan Lu, Chuan-Mo Lee, Jing-Houng Wang, Tsung-Hui Hu, Chao-Hung Hung, Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung 833, Taiwan
Author contributions: Chen CH performed the literature review and wrote the paper; Chiu YC, Lu SN, Lee CM, Wang JH and Hu TH contributed to acquisition of data; and Hung CH performed the critical revision.

Correspondence to: Chao-Hung Hung, MD, Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, 123 Ta Pei Road, Kaohsiung 833, Taiwan. chh4366@yahoo.com.tw

Telephone: +886-7-7317123 Fax: +886-7-7318762

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Abstract

Quantification of hepatitis B surface antigen (HBsAg) has been suggested to be helpful in the management of chronic hepatitis B (CHB) patients. Nucleos(t)ide analogs (NAs) are the therapy of choice for CHB and are used in the majority of CHB patients. NAs are able to induce hepatitis B virus (HBV) viral suppression, normalization of alanine aminotransferase (ALT) levels, and improvement in liver histology. Automated quantitative assays for serum HBsAg have recently become available, facilitating standardized quantification of serum HBsAg. This has led to increased interest in the clinical application of quantitative serum HBsAg for predicting therapeutic response to NAs. Recent studies have shown that a decline in serum HBsAg levels in patients receiving peginterferon may signal successful induction of immune control over HBV, and can therefore be used to predict therapeutic response. NA treatment typically induces a less rapid decline in HBsAg than interferon

treatment; it has been estimated that full HBsAg clearance can require decades of NA treatment. However, a rapid HBsAg decline during NA therapy may identify patients who will show clearance of HBsAg. Currently, there is no consensus on the clinical utility of serum HBsAg monitoring for evaluating patient responses to NA therapy. This review focuses on recent findings regarding the potential application of HBsAg quantification in the management of CHB patients receiving NA therapy.

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Key words: Alanine aminotransferase; Hepatitis B virus; Hepatitis B surface antigen; Nucleos(t)ide analogs; Virological response

Core tip: Patients receiving nucleos(t)ide analog (NA) treatment typically exhibit slow declines in serum hepatitis B surface antigen (HBsAg), with many patients requiring decades of treatment to achieve HBsAg clearance. However, a low baseline HBsAg level or a rapid reduction in HBsAg during NA therapy may identify patients who will show HBsAg clearance, and predict virological response or hepatitis B e antigen (HBeAg) loss/seroconversion in HBeAg-positive patients. Viral breakthrough due to drug resistance can increase HBsAg titers. Among Asian patients, HBsAg levels of < 100-200 IU/mL at the end of treatment may predict lower risk of hepatitis B virus relapse and cessation of treatment can be considered in HBeAg-negative patients.

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INTRODUCTION

Chronic hepatitis B (CHB) is an important global health problem, affecting over 350 million people worldwide^[1]. Chronic hepatitis B virus (HBV) infection may be asymptomatic in carriers, or may progress to severe chronic liver disease, including cirrhosis and hepatocellular carcinoma^[2-4]. Since the discovery of hepatitis B surface antigen (HBsAg) by Blumberg in 1965, HBsAg has been used as a diagnostic marker for overt HBV infection^[5]. Automated quantitative assays for serum HBsAg have recently become available, facilitating standardized quantification of serum HBsAg. This has led to increased interest in the clinical application of quantitative serum HBsAg levels for predicting therapeutic response^[6,7]. Our previous study in asymptomatic carriers found a correlation between HBsAg and HBV DNA levels^[8]. Similarly, changes in intrahepatic covalently closed circular DNA (cccDNA) levels were found to be correlated with reduced serum HBsAg titer in patients receiving adefovir monotherapy or peginterferon plus adefovir or lamivudine therapy^[9-11]. Further, a positive correlation has been observed between HBsAg titer and serum HBV DNA and liver cccDNA in hepatitis B e antigen (HBeAg)-positive patients^[12]. In recent years, many studies have been performed to evaluate the use of serum HBsAg levels to predict treatment response in CHB. Several studies have shown that reduction in serum HBsAg levels in patients treated with peginterferon may signal the successful induction of immune control over HBV, and can consequently be used to predict treatment response^[13-15]. Nucleos(t)ide analogs (NAs), the therapy of choice for CHB, are well tolerated and have a good safety profile. To date, the NAs lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir have been approved for therapeutic use in most countries. NAs are able to induce suppression of HBV viral activity, normalization of alanine aminotransferase (ALT) levels, and improvement in liver histology. In patients with advanced liver disease, NA therapy has been shown to suppress viral replication and prevent hepatic decompensation^[16-19]. However, emerging antiviral drug resistance is a major obstacle to the success of NA therapy for HBV^[20-22]. These compounds vary considerably in their potency and their ability to suppress the emergence of resistant strains. Long-term entecavir and tenofovir therapy have been shown to improve fibrosis in patients with CHB^[23,24]. NA therapy works by competitively inhibiting HBV polymerase activity, which is part of a viral replication pathway that is separate from HBsAg production^[25]. Although treatment with NAs can induce a marked reduction in HBV DNA levels, the effect on serum HBsAg levels is indirect and may be very limited. Consequently, the decline in HBsAg during NA treatment is considerably slower than that observed for HBV DNA^[13,26,27]. At present, there is limited agreement regarding the clinical utility of serum HBsAg monitoring during and after cessation of NA therapy. In this review, we summarize recent findings concerning the use of HBsAg quantification for predicting therapeutic response in

CHB patients treated with NAs.

Comparison of HBsAg kinetics in patients receiving interferon vs NA therapy

A number of studies have compared the effects of interferon and NA on HBsAg kinetics^[13,15,28]. For example, Brunetto *et al.*^[13] examined HBsAg kinetics in a cohort of 386 HBeAg-negative CHB patients treated with peginterferon alfa-2a, with lamivudine, or with both agents. A significant on-treatment decline in HBsAg was observed during treatment with peginterferon alfa-2a, alone or combined with lamivudine (mean reduction at week 48 was -0.71 and -0.67 log IU/mL, respectively). No significant reduction was observed during treatment with lamivudine alone (-0.02 log IU/mL, $P < 0.001$). In addition, a significantly higher proportion of patients treated with peginterferon alfa-2a (21%) or peginterferon alfa-2a plus lamivudine (17%) achieved HBsAg levels of < 100 IU/mL at the end of treatment, compared with the lamivudine-only group (1%)^[13]. Manesis *et al.*^[15] compared the rates of on-treatment decline in HBsAg levels in patients receiving lamivudine treatment (median duration of 33 mo) *vs* interferon treatment. Patients treated with interferon showed a more rapid decrease in serum HBsAg than those treated with lamivudine. Based on these results, it was estimated that 5.4 years of sustained response to interferon or 10.6 years of effective lamivudine therapy would be required to achieve clearance of HBsAg^[15]. Reijnders *et al.*^[26] compared HBsAg kinetics in CHB patients receiving either peginterferon or entecavir monotherapy. Their data showed that, in HBeAg-positive patients, peginterferon treatment induced a more rapid decline in HBsAg than entecavir treatment (mean reduction of 0.94 log IU/mL *vs* 0.38 log IU/mL, respectively, at week 48, $P = 0.07$). In HBeAg-negative patients, peginterferon induced a significant decrease in HBsAg, while entecavir treatment did not significantly decrease HBsAg (0.56 log IU/mL *vs* -0.10 log IU/mL, $P < 0.001$)^[15].

The above studies suggest that HBsAg reduction during NA therapy is slower and less pronounced than during interferon treatment, despite the marked effect of NA therapy on HBV DNA levels. This is because NA blocks only the viral reverse transcriptase, which inhibits HBV DNA synthesis, but does not directly affect either cccDNA or HBsAg. In contrast, interferon has both direct and immune-mediated antiviral activity. It seems likely that the immune modulating effects of interferon are responsible for its dramatic effects on HBsAg production and secretion^[6] (Table 1).

Use of HBsAg to predict virological response or HBeAg loss/seroconversion during NAs therapy

In recent years, many studies have showed that the on-treatment level or the dynamics of HBsAg may be used to predict treatment response in peginterferon-treated CHB patients^[13-15]. However, it remains unclear whether this finding is also applicable in the context of NA treatment. In a small study, HBsAg was measured in 20 CHB

Table 1 Comparison of hepatitis B surface antigen kinetic between interferon and nucleos(t)ide analogues

Interferon <i>vs</i> NA	HBeAg status	Mean decline of HBsAg (log IU/mL) at week 48		Ref.
Peginterferon alfa-2a + lamivudine <i>vs</i> lamivudine	HBeAg (-) patients	0.71 <i>vs</i> 0.02	$P < 0.001$	[13]
Peginterferon alfa-2a <i>vs</i> lamivudine alone		0.67 <i>vs</i> 0.02	$P < 0.001$	
Peginterferon <i>vs</i> entecavir	HBeAg (+) patients	0.94 <i>vs</i> 0.38	$P = 0.07$	[26]
	HBeAg (-) patients	0.56 <i>vs</i> -0.10	$P < 0.001$	

NAs: Nucleos(t)ide analogues; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen.

patients before and during lamivudine treatment^[28]. In this study, an increase in HBsAg titer was found to precede the emergence of drug-resistant variants^[28]. Another study analyzed 42 HBeAg-negative patients who received long-term lamivudine monotherapy^[29]. HBsAg levels decreased only in long-term on-treatment responders, whereas no significant change was observed in patients with lamivudine-resistant mutant HBV. Failure to achieve a decrease of 0.7 log IU/mL in HBsAg at month 6 of lamivudine therapy had a positive predictive value of 92% for developing virological breakthrough, and a negative predictive value of 100%^[29]. In HBeAg-positive patients with serum HBV DNA levels of < 2000 IU/mL after 6 mo of NA therapy, a baseline HBsAg level of ≥ 20000 IU/mL was the only risk factor significantly associated with virological breakthrough^[30]. The available evidence suggests that monitoring of serum HBsAg concentration during treatment is helpful for evaluating patient response to lamivudine treatment, as well as for early detection of lamivudine-resistant strains.

The NAs entecavir and tenofovir are now recommended as first-line treatment for CHB, due to their high potency and high genetic barrier to resistance. Given their clinical importance, it is of interest to determine whether HBsAg levels or kinetics can be used to predict either VR or HBeAg loss/seroconversion during entecavir or tenofovir therapy. In one study, HBsAg levels were analyzed in 95 CHB patients treated with entecavir for 2 years^[31]. For the HBeAg-positive group of patients (60%, $n = 57$), a baseline HBsAg cutoff value of 9550 IU/mL yielded the highest predictive value for VR, with a sensitivity of 86.8% and a specificity of 78.9%. However, neither baseline HBsAg nor reduction in HBsAg were predictive of VR in HBeAg-negative patients^[31]. Another study analyzed HBsAg in 101 treatment-naïve CHB patients who received entecavir for 24 mo^[32]. In HBeAg-positive patients, a HBsAg level of < 3000 IU/mL at 3 mo of treatment was found to be an independent predictor of HBeAg loss/seroconversion at 12 mo. After 24 mo of treatment, HBsAg level at baseline was an independent predictor of HBeAg loss/seroconversion, while a HBsAg level of < 3000 IU/mL at 3 mo of treatment was an independent predictor for achieving VR. However, in HBeAg-negative patients, HBsAg was not a significant factor for predicting VR^[32]. Another study examined a cohort of 50 treatment-naïve patients who were treated with entecavir therapy for more than 2 years. All patients carried HBV genotype C, and almost

half ($n = 24$) were HBeAg-positive. Interestingly, low baseline HBsAg levels were the most significant predictor of VR at year 2 of treatment, for all patients, regardless of HBeAg status^[33]. In a study involving 82 HBeAg-positive CHB patients who received entecavir therapy for ≥ 3 years, patients who achieved VR had higher levels of HBsAg, both at baseline and during treatment, than those who did not achieve VR. However, HBsAg reduction from baseline was not significantly different between the VR and the non-VR groups. In contrast, patients who achieved HBeAg seroconversion had higher baseline levels of HBsAg and showed more marked HBsAg decline on-treatment than those who did not achieve HBeAg seroconversion^[34]. Another analysis involved 55 CHB patients who received entecavir for more than 2 years, 23 of whom were HBeAg-positive. Patients with a high baseline HBsAg level (> 10000 IU/mL) had a lower rate of VR at year 1 (37.5% *vs* 89.7%, $P < 0.001$) and at year 2 (56.2% *vs* 94.9%, $P = 0.001$). However, a substantial (> 1 log) reduction in HBsAg from baseline to 6 mo was not predictive of HBeAg loss in HBeAg-positive patients, or of VR in all patients^[35]. Another study analyzed HBsAg in 104 patients coinfecting with HBV and human immunodeficiency virus (HIV) who received tenofovir as part of a highly active antiretroviral therapy (HAART) regimen. Of these patients, 66 were HBeAg-positive. In this study, patients with HBeAg loss exhibited more marked reductions in HBsAg, compared to patients who remained HBeAg-positive (2.5 log IU/mL *vs* 1.8 log IU/mL, $P < 0.001$) after 6 years of therapy. However, no significant difference was observed in baseline HBsAg levels between HBeAg-positive and HBeAg-negative patients^[36].

Fung *et al.*^[37] analyzed HBsAg levels in 166 CHB patients (68 of whom were HBeAg-positive) over 2 years of entecavir treatment. At year 2, 102 patients (61%) showed no significant change (< 0.5 log IU/mL difference) in HBsAg, 50 (30%) showed a significant decline (≥ 0.5 log IU/mL decrease), and 14 (9%) showed a significant increase (≥ 0.5 log IU/mL increase). Early reductions in HBsAg levels at 12 or 24 wk were not associated with HBV DNA suppression or HBeAg seroconversion after two years of treatment^[37]. Another recent study involved 70 patients who were continuously treated with lamivudine for at least 10 years and maintained favorable VR (HBV DNA < 2000 IU/mL) throughout the course of therapy. The median rate of HBsAg reduction in this cohort was 0.104 log IU/mL per year. No significant differences were found when comparing either HBeAg-

Table 2 Hepatitis B surface antigen predict virological response or hepatitis B e antigen loss/seroconversion during nucleos(t)ide analogues therapy

NAs	Treatment duration	Case number	Comments	Ref.
Entecavir	2 yr	95	HBeAg (+) patients: baseline HBsAg cutoff level of 9550 IU/mL yielded the highest predictive value in predicting the VR	[31]
Entecavir	2 yr	101	HBeAg (-) patients: baseline HBsAg or HBsAg decline levels could not predict VR HBeAg (+) patients: HBsAg level at baseline was an independent factor of HBeAg loss/seroconversion HBsAg level < 3000 IU/mL at 3 mo of treatment was an independent factor for achieving VR	[32]
Entecavir	More than 2 yr	50	HBeAg (-) patients: HBsAg levels could not predict VR Low baseline HBsAg levels were the most significant factor for achieving VR at year 2 of treatment	[33]
Tenofovir	6 yr	104 HBV + HIV	A higher level of HBsAg decline in patients with HBeAg loss compared to patients remaining HBeAg-positive (2.5 log IU/mL vs 1.8 log IU/mL, $P < 0.001$) Baseline HBsAg levels could not predict HBeAg loss	[36]

VR: Virological response; NAs: Nucleos(t)ide analogues; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; HIV: Human immunodeficiency virus.

positive vs HBeAg-negative patients, or those with detectable vs undetectable viremia during therapy^[38].

For lamivudine treatment, there is evidence that monitoring of serum HBsAg concentrations is helpful for the early detection of drug-resistant strains. For entecavir and tenofovir treatment, the majority of studies indicate that monitoring of serum HBsAg levels may be useful for predicting VR or HBeAg loss/seroconversion in HBeAg-positive patients, but not in HBeAg-negative patients. The lack of predictive value for HBeAg-negative patients could be due to the very high rates of VR obtained after 2 years of entecavir or tenofovir therapy. Whether baseline HBsAg levels or rates of HBsAg reduction during treatment can be used to predict treatment response in HBeAg-positive patients is still an open question. Additional studies will be needed to resolve this issue (Table 2).

Use of HBsAg to predict HBsAg loss during NA therapy

There is evidence that CHB patients who show loss of HBsAg may achieve more favorable outcomes^[39,40]. Previous longitudinal studies have estimated the annual rate of HBsAg loss at approximately 0.4%-2.3%, depending on age and status of liver disease^[41-45]. In a longitudinal study conducted in Taiwan, which involved a total of 1965 HBeAg-negative patients with normal ALT levels, Chu *et al.*^[42] reported an annual HBsAg loss rate of 1.15%. A large community-based cohort study also found that, in adult patients with an undetectable viral load (< 60 IU/mL), the annual rate of HBsAg loss was 5.76%^[43]. A number of studies have attempted to address whether quantitative HBsAg levels can be used to predict HBsAg loss during the natural course of HBV infection. A recent study showed that serum HBsAg levels of < 100 IU/mL or 100-999 IU/mL at 1 year after spontaneous HBeAg seroconversion were associated with higher HRs of HBsAg loss (24.3 and 4.4, respectively) than higher HBsAg levels^[44]. Another study analyzed data for 688 HBeAg-negative patients who had HBV DNA levels of < 2000 IU/mL at baseline. The annual clearance rate of

HBsAg reached 7% in patients with HBsAg levels of < 10 IU/mL (HR = 13.2, 95%CI: 8.1-21.5 when compared to those with HBsAg levels of ≥ 1000 IU/mL). These large-scale studies provide evidence for a relationship between HBsAg levels and HBsAg loss during the natural course of HBV infection^[45].

To achieve sustained viral suppression, a prolonged period of NA treatment is usually required. The rate of HBsAg clearance induced by oral NA treatment is low and loss of HBsAg is generally only seen after many years of therapy^[46,47]. Several groups have investigated the use of the decline in HBsAg levels to predict the duration of continuous treatment required to clear HBsAg. Estimates of time to HBsAg clearance span several decades. For example, one longitudinal study followed 30 CHB patients treated with different NAs until their HBV DNA levels became undetectable (median duration of 102 mo)^[48]. The mean HBsAg level at the time when HBV DNA became undetectable was 3.29 ± 0.49 log IU/mL, and the mean slope (representing the rate of HBsAg decline) was -0.007 ± 0.007 log IU/mo. Thus, the predicted median time to HBsAg loss was 52.2 years^[48]. Another recent study analyzed HBsAg decline in 75 CHB patients with VR to entecavir or tenofovir. The decrease in HBsAg 2 years after VR was most pronounced in HBeAg-positive patients (0.81 log IU/mL), compared with HBeAg-negative patients (0.15 log IU/mL). The predicted median time to HBsAg loss was 36 years for HBeAg-positive patients and 39 years for HBeAg-negative patients^[49]. Thus, most patients receiving NA treatment are likely to require decades of therapy to achieve HBsAg loss.

Another key issue is whether quantitative HBsAg levels could be used to predict HBsAg loss during NA treatment. Wursthorn *et al.*^[50] analyzed HBsAg in 162 HBeAg-positive patients treated with telbivudine for at least 3 years. All patients maintained HBV DNA levels of < 60 IU/mL after 2 years of therapy. Nine patients (6%) developed HBsAg loss (genotype A, $n = 2$; genotype C, $n = 5$; genotype D, $n = 2$). A rapid HBsAg decline of > 1 log

Table 3 Hepatitis B surface antigen predict hepatitis B surface antigen loss during nucleos(t)ide analogues therapy

NAs	Treatment duration	Case number	Condition of HBsAg predict HBsAg loss	Ref.
Telbivudine	more than 3 yr	162 HBeAg (+)	HBsAg decline ≥ 1 log after 1 yr of treatment	[50]
Tenofovir	3 yr	263 HBeAg (+)	Steeper declines in HBsAg (-2.41 log ₁₀ IU/mL vs -0.20 log ₁₀ IU/mL) at month 6	[51]
Tenofovir	6 yr	104 HBV + HIV	HBsAg decline ≥ 2 log IU/mL at month 6	[36]
Lamivudine	more than 10 yr	70	Baseline HBsAg < 1000 IU/mL and on-treatment reduction of HBsAg > 0.166 log IU/mL per year	[38]
Lamivudine as their first drug	9 yr	791	HBeAg (+) patients: HBsAg decline ≥ 0.5 log IU/mL within 6 mo HBeAg (-) patients: HBsAg decline at 6 mo and baseline HBsAg levels of < 730 IU/mL	[53]

NAs: Nucleos(t)ide analogues; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; HIV: Human immunodeficiency virus.

after 1 year of treatment was predictive of HBsAg loss during telbivudine treatment. Eight out of 32 patients with a rapid HBsAg decline *vs* none out of 56 patients with steady HBsAg levels, achieved HBsAg loss at year 3 ($P = 0.0024$)^[50]. Similarly, in a registration study of tenofovir, Heathcote *et al.*^[51] found that 20 of 263 HBeAg-positive patients (genotype A, $n = 12$; genotype D, $n = 7$; genotype F, $n = 1$) who achieved HBsAg clearance after 144 wk of treatment experienced a greater median change from baseline in HBsAg levels at week 24 (-2.41 log₁₀ IU/mL *vs* -0.20 log₁₀ IU/mL). Marcellin *et al.*^[52] also reported that patients with HBsAg loss tended to have higher baseline HBsAg levels and a more rapid decline in HBsAg levels as compared to those who failed to lose HBsAg on 4-year tenofovir treatment. Another study analyzed 104 patients coinfecting with HBV and HIV who received tenofovir as part of a HAART regimen^[36]. Five (8%) of the 66 HBeAg-positive patients in this cohort (genotype A, $n = 3$; genotype D, $n = 1$; undetermined genotype, $n = 1$) achieved HBsAg seroclearance. A decline in HBsAg of ≥ 2 log IU/mL at month 6 was highly predictive of HBsAg seroclearance; 71% of these patients achieved HBsAg seroclearance, whereas none of the patients with a decline of < 2 log IU/mL achieved seroclearance^[36].

Two recent studies also concluded that low baseline HBsAg levels and rapid HBsAg decline were predictive for HBsAg loss during long-term lamivudine treatment. Seto *et al.*^[38] analyzed data for 70 patients who were continuously treated with lamivudine for at least 10 years and maintained favorable VR (defined as HBV DNA < 2000 IU/mL) throughout therapy. Seven (10%) patients achieved HBsAg seroclearance (genotype B, $n = 2$; genotype C, $n = 4$; undetermined genotype, $n = 1$). Baseline HBsAg levels of < 1000 IU/mL and on-treatment HBsAg reductions of > 0.166 log IU/mL per year were found to be optimal cutoff levels for predicting subsequent HBsAg seroclearance. Hosaka *et al.*^[53] analyzed data for 791 patients who received lamivudine as their first drug for 9 years; 442 of these patients were HBeAg-positive at baseline. HBsAg clearance was observed in 18 (4.1%) of the HBeAg-positive patients and 20 (5.7%) of the HBeAg-negative patients (genotype A, $n = 8$; genotype B, $n = 3$; genotype C, $n = 25$; genotype D, $n = 1$; undetermined genotype, $n = 1$). For HBeAg-positive

patients, previous interferon therapy, HBV genotype A, a ≥ 0.5 log IU/mL reduction in HBsAg level within 6 mo, and clearance of HBeAg at 6 mo were independent factors predictive of HBsAg loss. For HBeAg-negative patients, HBV genotype A, a decline in HBsAg at 6 mo, and a baseline HBsAg level of < 730 IU/mL were independent factors found to be predictive of HBsAg loss^[53].

However, in a German study of 95 CHB patients on NA therapy, an early HBsAg decrease after 6 mo of NA therapy was not associated with HBsAg loss. In contrast, 42% of patients with a HBsAg decline of > 0.5 log IU/mL in the 2 years after VR (defined as HBV DNA levels of < 100 IU/mL) subsequently achieved HBsAg loss^[54].

Most of the studies described above suggest that an early decline in HBsAg levels may predict immune control in patients treated with NA, and that this decline may be predictive of subsequent HBsAg loss. Some studies suggested that low baseline HBsAg levels might also be predictive of subsequent HBsAg loss. However, there is currently no consensus on the optimal cut-off values for baseline HBsAg (*e.g.*, < 1000 IU/mL) or early HBsAg decline (*e.g.*, 1 or 2 log IU/mL). Most patients who achieved NA-induced HBsAg loss had HBV genotype A or D infections. NA-induced HBsAg clearance appears much rarer and requires a longer duration of treatment in Asian patients with genotype B or C infections (Table 3).

Use of HBsAg to predict HBsAg loss and HBV relapse after cessation of NA therapy

Oral NA therapy is very effective for viral suppression and normalization of liver enzymes. However, virological relapse is common despite the ability to achieve and maintain on-treatment viral suppression^[17,55-57], because of the persistence of cccDNA in the nuclei of infected hepatocytes after cessation of therapy. In a recent study, 13 (72%) of 18 HBeAg-negative patients who achieved a sustained response after cessation of adefovir therapy also showed successful clearance of HBsAg^[58]. This suggests that long-term anti-viral therapy may not be necessary in all cases. Due to the cost of long-term oral antiviral therapy, cessation of NA treatment may be considered in a subgroup of patients. Therefore, it will be important to identify useful parameters that can aid in the decision to stop NA therapy, thereby reducing the burden of long-term therapy. It will be also of interest to identify

suitable cut-off values for both serum HBsAg reduction and HBsAg levels (baseline or on-treatment), that indicate effective immune control. This may help identify cases in which termination of antiviral therapy is possible with low risk of reactivation.

In a study of 17 HBeAg-positive patients who received telbivudine treatment for 104 wk, serum HBsAg levels of < 100 IU/mL at the end of treatment were found to be highly predictive of sustained response after 2 years off-treatment. HBsAg reductions of > 0.8 and > 1 log IU/mL from baseline to weeks 24 and 52 of treatment were found to be more predictive of sustained response than HBV DNA decline^[59]. Another study analyzed 51 HBeAg-positive CHB patients who achieved HBeAg loss/seroconversion and completed \geq 12 mo of additional therapy^[60]. Sustained virological response (SVR) was defined as maintenance of HBV DNA at < 10000 copies/mL until 6 or 12 mo off-treatment, without reappearance of HBeAg. In this study, neither HBsAg levels at baseline or on-treatment, nor HBsAg decline were significant predictive factors for SVR at 12 mo off-treatment^[60].

The frequency of virological relapse appears variable. In a study conducted in China and Hong Kong, 84 CHB patients (69 treatment-naïve and 15 lamivudine-resistant cases) who stopped oral antiviral therapy (lamivudine, adefovir or entecavir) in accordance with 2008 Asian Pacific Association for the Study of the Liver (APASL) guidelines were analyzed. Only 1 of the 11 patients who had achieved HBsAg levels of < 2 log IU/mL at the end of treatment experienced virological relapse (HBV DNA levels of > 1000 copies/mL)^[61]. In another study from Hong Kong, 53 HBeAg-negative patients on lamivudine treatment for a mean of 34 mo were analyzed. Levels of HBsAg, but not HBV DNA, were more strongly associated with attainment of SVR (HBV DNA \leq 200 IU/mL) at 12 mo off-treatment. All five patients who had HBsAg levels of \leq 100 IU/mL and HBsAg reduction of > 1 log at the end of treatment achieved SVR at 12 mo off-treatment; in contrast, all 40 patients who had HBsAg levels of > 100 IU/mL and HBsAg reduction of \leq 1 log did not achieve SVR at 12 mo off-treatment. The end-of-treatment HBsAg response was also predictive of SVR and HBsAg loss up to 5 years after stopping lamivudine therapy^[62].

In our recent study^[63], we analyzed 188 treatment-naïve CHB patients (83 HBeAg-positive, 105 HBeAg-negative patients) treated with lamivudine. Post-treatment HBV relapse was defined as a serum HBV DNA level of > 2000 IU/mL. We found that, at the end of treatment, a HBsAg cutoff value of < 300 IU/mL was able to predict HBsAg loss in 55.6% (5/9) of HBeAg-positive patients. HBsAg was not a significant predictor for post-treatment HBV relapse in HBeAg-positive patients. In HBeAg-negative patients, HBsAg cutoff values of < 120 and < 200 IU/mL predicted off-treatment HBsAg loss in 79.2% (19/24) of cases and sustained response in 93.3% (28/30) of cases, respectively^[63]. Entecavir is a potent NA

with high genetic barrier to drug resistance. In our recent study^[64], a total of 142 CHB patients (46 HBeAg-positive, 96 HBeAg-negative patients) treated with entecavir were analyzed, to determine whether HBsAg quantification could predict HBV reactivation after cessation of treatment. Treatment duration was 153.6 ± 43.9 wk, and all patients fulfilled the APASL 2012 stopping criteria. In HBeAg-positive patients, a baseline HBsAg level of < 4000 IU/mL was the optimal cut-off value for predicting virological relapse (HBV DNA levels of > 2000 IU/mL) and clinical relapse (HBV DNA levels of > 2000 IU/mL and ALT levels of more than twice the upper normal limit). In HBeAg-negative patients, end-of-treatment HBsAg levels of < 200 and < 500 IU/mL were the optimal cut-off values for predicting virological and clinical relapse respectively. HBsAg decline from baseline to month 12 or end of treatment was not a significant predictor for virological relapse.

A recent study from Taiwan analyzed data for 95 patients who were treated with entecavir for a median duration of 721 (395-1762) d, and who fulfilled the 2012 APASL stopping criteria. In this study, neither HBsAg levels at baseline or end of treatment nor HBsAg decline were capable of predicting clinical relapse after one year off-treatment^[65].

Given the studies discussed above, HBsAg levels at the end of treatment may be useful in HBeAg-negative patients for predicting HBsAg loss or HBV reactivation after cessation of NA treatment. End-of-treatment cut-off values of HBsAg < 100 or < 200 IU/mL have been used in many of the existing studies, with reasonable success. However, it remains unclear whether baseline or end-of-treatment HBsAg levels are able to predict HBV reactivation in HBeAg-positive patients after cessation of NA treatment. In addition, it remains to be determined whether the kinetics of HBsAg decline can predict HBV reactivation off-treatment. To date, most studies have been conducted in Asian populations, in which the HBV genotypes B and C are predominant. It is unclear whether the same HBsAg cut-offs are applicable to other HBV genotypes (Table 4).

OTHER ISSUES

Boglione *et al.*^[66] have examined HBsAg kinetics in 134 treatment-naïve patients treated with different NAs (lamivudine, adefovir, telbivudine, entecavir and tenofovir) for at least 2 years. All patients had similar characteristics: HBeAg-negative, HBV genotype D, and persistently undetectable HBV DNA levels. Tenofovir treatment resulted in the best serological response with respect to HBsAg reduction (0.45 log IU/mL after 2 years), while entecavir produced a moderate serological response (0.38 log IU/mL). Telbivudine showed the poorest serological response overall (0.12 log IU/mL), while adefovir exhibited a better serological (0.22 log IU/mL) than virological response. These results suggest that, in order to induce a substantial decrease in HBsAg, HBeAg-negative patients

Table 4 Hepatitis B surface antigen predict hepatitis B virus relapse after stopping nucleos(t)ide analogues therapy

Patients	NAs and treatment duration	Definition of HBV relapse or sustained response (SR)	Comments	Ref.
17 HBeAg (+) patients	telbivudine for 104 wk	SR: HBV DNA < 300 copies/mL, HBeAg seroconversion, ALT normalization at 2 yr off-treatment	HBsAg levels < 100 IU/mL at the end of treatment and HBsAg decline of > 0.8 and > 1 log IU/mL at treatment weeks 24 and 52 were predictive of SR	[59]
51 HBeAg (+) patients	lamivudine, adefovir or entecavir Stop treatment: HBeAg loss/seroconversion and \geq 12 mo of additional therapy	SR: HBV DNA levels < 10000 copies/mL until 6 or 12 mo off-treatment without reappearance of HBeAg	A decline in HBsAg of 0.5 log IU/mL at 6 mo was the independent factor for SR at 6 mo off-treatment A decline in HBsAg was not a significant factor for SR at 12 mo off-treatment	[60]
41 HBeAg (+), 43 HBeAg (-) patients	lamivudine, adefovir or entecavir Stop treatment: according to the 2008 APASL guidelines	Virological relapse: HBV DNA > 1000 copies/mL after discontinuation of treatment	HBsAg levels < 100 IU/mL at the end of treatment was predictive of SR	[61]
53 HBeAg (-) patients	Lamivudine for 34 \pm 23 mo	SR: HBV DNA \leq 200 IU/mL at 12 mo off-treatment.	Combined HBsAg \leq 100 IU/ml and HBsAg reduction > 1 log at the end of treatment were predictive of SR	[62]
83 HBeAg (+), 105 HBeAg (-) patients	Lamivudine for 89.3 \pm 35.9 wk	SR: serum HBV DNA to \leq 2000 IU/mL after discontinuation of treatment	HBeAg (+) patients: HBsAg (cut-off value of < 300 IU/mL) at the end of treatment was predictive of HBsAg loss HBeAg (-) patients: HBsAg (cut-off values of < 120 and < 200 IU/mL) at the end of treatment was predictive of HBsAg loss and SR respectively.	[63]
46 HBeAg (+), 96 HBeAg (-) patients	Entecavir for 153.6 \pm 43.9 wk Fulfilled the stopping criteria of the APASL 2012	Virological relapse: HBV DNA > 2000 IU/mL. Clinical relapse: HBV DNA > 2000 IU/mL and ALT > 2 X ULN	HBeAg (+) patients: HBsAg (cut-off value of < 4000 IU/mL) at baseline was predictive of virological and clinical relapse HBeAg (-) patients: HBsAg (cut-off values of < 200 and < 500 IU/mL) at the end of treatment were predictive of virological and clinical relapse respectively	[64]

HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; APASL: Asian pacific association for the study of the liver; ALT: Alanineaminotransferase; ULN: Upper limit of normal.

infected with HBV genotype D should be treated with more potent NAs, such as entecavir or tenofovir^[67].

A recent study analyzed data for 142 Asian CHB patients who received tenofovir, with or without lamivudine, for up to 3 years^[67]. Patients also had at least 6 mo exposure to other NAs. Compared to patients with baseline HBsAg levels of < 3 log IU/mL, patients with baseline HBsAg levels of \geq 3 log IU/mL showed a greater median rate of HBsAg reduction over 3 years of tenofovir treatment. Among patients with 3 years of treatment, there was a significantly higher median rate of HBsAg reduction during the first year than during the second and third years. This pattern of HBsAg decline could partially explain the rarity of HBsAg seroclearance during NA therapy in the Asian populations studied^[67].

CONCLUSION

Although NAs are the preferred therapy for CHB infection, their effect on serum HBsAg levels is indirect and relatively slow. It has been estimated that HBsAg clearance on NA treatment may require decades of therapy. In addition, the decline in serum HBsAg induced by NA treatment often does not correlate with changes in HBV DNA levels. However, there is evidence that a low baseline HBsAg level and/or a rapid decline in serum HBsAg levels during NA therapy are characteristics that may identify patients who will show clearance of HBsAg. These two factors may also predict HBeAg-positive

patients who will achieve virological response or HBeAg loss/seroconversion. An increase in HBsAg titer may be indicative of viral breakthrough, which is generally due to drug resistance. Among Asian patients (most of whom carry HBV genotypes B and C), an end-of-treatment HBsAg level of < 100 or < 200 IU/mL may predict a lower risk of HBV relapse, and cessation of treatment can be considered in HBeAg-negative patients. However, it remains unclear whether HBsAg levels, either at baseline or at the end of treatment, are also capable of predicting HBV relapse in HBeAg-positive patients after cessation of NA treatment. Since HBsAg kinetics is known to be influenced by HBV genotype, it will be important to validate these findings in larger cohorts that provide data for various HBV genotypes. Monitoring of serum HBsAg levels at baseline and during treatment can provide complementary information to HBV DNA measurements, and may help to improve the prediction of initial treatment response, HBsAg loss and/or sustained off-treatment response to NA therapy.

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