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Review Article

Clinical Implications of HBsAg Quantification in Patients with Chronic Hepatitis B

Mauro Viganò, Pietro Lampertico[1]

Hepatology Unit, Ospedale San Giuseppe, [1]1st Division of Gastroenterology, Fondazione Cà Granda IRCCS Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milano, Italy

Address for correspondence:
Dr. Pietro Lampertico, 1st Division of Gastroenterology, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Università di Milano, Via F. Sforza 35 - 20122 Milan, Italy.
E-mail: pietro.lampertico@unimi.it

ABSTRACT

Quantification of serum hepatitis B surface antigen (HBsAg) helps the management of patients with chronic hepatitis B virus (HBV) infection. Median HBsAg levels differ significantly during the natural history of HBV infection, progressively declining from immune tolerance to inactive phase. The combination of an HBsAg <1000 IU/mL and HBV DNA <2000 IU/mL at a single time point accurately identifies true inactive carriers. During antiviral treatment, HBsAg levels decline more rapidly in patients under peg-interferon (Peg-IFN) than in those under nucleos(t)ide analogues (NUC), and in responders to peg-IFN compared to non responders suggesting that a response-guided therapy in both HBeAg-positive and -negative patients treated with Peg-IFN could improve to cost-effectiveness of this therapeutic approach. Given the low rates of HBsAg clearance on NUC therapy, new studies to test whether Peg-IFN and NUC combination fosters HBsAg decline in long-term responders to NUC, are being explored.

Key Words: Chronic hepatitis B, HBsAg quantification, interferon

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Serum hepatitis B surface antigen (HBsAg) is a reliable marker of overt hepatitis B virus (HBV) infection, whereas anti-HBs seroconversion represents the ultimate goal of antiviral therapy, that is, the closest outcome to cure infection.[1,2] Quantification of serum HBsAg has been recently standardized by automated quantitative assays leading to an increased interest in the clinical utilization of this marker.[3,4] HBsAg serum levels result from a balance between virus biology and a host's immune system as well as the indirect expression of transcriptionally active covalently closed circular DNA (cccDNA) rather than the product of the viral replication.[5] Several studies, particularly those with Peg-Interferon, have shown kinetics of HBsAg to predict a response to antiviral therapy, the predictive value of HBsAg being important for both treatment individualization[6-8] and interpretation of the phases of HBV infection in untreated patients.[9-11]

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In this review we aim to analyze the recent findings on HBsAg quantification and its clinical use in the management of patients with chronic hepatitis B infection.

HBSAG QUANTIFICATION IN UNTREATED PATIENTS

Chronic HBV infection runs through four chronologic phases: an initial "immune tolerance phase" characterized by serum HBeAg and high viremia accompanied by null or minimal histologic damage. The second phase is the "immune clearance phase," whereby the immune system recognizing HBV as a foreign invader causes extensive liver cell inflammation, that is, the HBeAg-positive chronic hepatitis. The third phase is the "inactive phase" in anti–HBe-positive patients showing persistently normal alanine aminotransferase (ALT) and low HBV DNA levels (<2000 IU/mL). The fourth phase is characterized by late reactivation of infection with persistently or intermittently increased HBV DNA and ALT levels accompanied by progressive liver damage, the so-called HBeAg-negative chronic hepatitis. While in most patients these phases occur in sequence, there are patients who apparently do not experience all phases like those persistently positive for HBeAg and those who remain persistently inactive carriers of HBsAg.

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While the median HBsAg levels differ significantly during the 4 phases of infection, serum HBsAg progressively declines from immune tolerance to inactive phase.[9-12] A longitudinal study of 68 HBeAg-negative untreated patients followed up for 99±16 months showed that a >1 $\log_{10}$ IU/mL HBsAg decline between the initial and last visits was associated with a higher HBsAg seroclearance rate and stronger viral suppression.[11] Two other studies in inactive carriers confirmed that HBsAg seroclearance was preceded by a greater HBsAg decline than in patients who remained HBsAg-seropositive.[13,14] Serum HBsAg level at 1 year after spontaneous HBeAg seroconversion may also be a harbinger of HBsAg clearance as shown by patients with HBsAg levels <100 IU/mL and between 100 and 999 IU/mL having higher hazard ratios of HBsAg loss (24.3 and 4.4, respectively) than patients with higher HBsAg levels.[15] Combining serum HBsAg with HBV DNA may provide stronger prediction of HBsAg seroclearance. This was the case in the study by Brunetto *et al*, who reported the combination of an HBsAg <1000 IU/mL and HBV DNA <2000 IU/mL at a single timepoint to accurately identify inactive carriers with a 88% positive (PPV) and a 97% negative predictive value (NPV).[13] In a longitudinal study in China, levels of HBsAg <1000 IU/mL and HBV DNA <2000 IU/mL were proved to predict the likelihood of HBsAg seroclearance, too, with a cumulative probability of HBsAg seroclearance at 5 years of 10%, which rose to 23% at 8 years.[16] In another study of 102 HBeAg-negative patients a cutoff of 2040 IU/mL of HBsAg had high sensitivity (87%) and high specificity (75%) to diagnose the inactive carrier state.[17] All these data need to be prospectively validated in larger sample size studies, including patients infected with all the major genotypes to establish reasonable intervals of surveillance in patients with chronic hepatitis B with respect to the risk of reactivation and seroclearance.

HBSAG QUANTIFICATION DURING ANTIVIRAL THERAPY

Peg-IFN therapy of HBeAg-positive patients

Reports of HBsAg decline in HBeAg-negative and -positive patients undergoing interferon-based therapy suggested the potential role of this marker for prediction of a treatment response.[7,18] HBsAg levels at the end of Peg-interferon (Peg-IFN) treatment has been shown to be significantly lower both in HBeAg-positive and negative patients with a sustained virologic response.[6,7,19] Owing to the fact that a rapid on-treatment decline of HBsAg levels predicts a sustained response, HBsAg levels at 12 or 24 weeks after the beginning of treatment have been associated with the identification of nonresponders or for tailoring treatment duration in responders. The lack of a significant decline of HBsAg at week 12 of Peg-IFN is a strong negative predictor of response in HBeAg-positive patients. This was demonstrated by Sonneveld *et al*, who showed that no decline in HBsAg levels at week 12 of Peg-IFNa-2b±lamivudine had a 3% chance of achieving a response, that is, HBeAg loss with HBV DNA <10,000 copies/mL 26 weeks after treatment, only (97% NPV).[20] The retrospective analysis of the Peg-IFNa-2a registration trial was less conclusive, as it demonstrated 18% of patients lacking a HBsAg decline at week 12 could achieve HBeAg loss and HBV DNA <2000 IU/mL 6 months posttreatment (82% NPV).[21] Whether these differences are explained by differences in HBV genotypes prevalence between studies, needs confirmation.

Piratvisuth *et al* demonstrated that patients with low HBsAg levels (<1500 IU/mL) at weeks 12 and 24 of Peg-IFNa-2a treatment had 57% and 54% chances of HBeAg seroconversion 6 months after completing treatment. Response rates were significantly lower in patients with intermediate HBsAg levels, that is, 1500–20,000 IU/mL (32 and 26%, respectively) or HBsAg levels >20,000 IU/mL (16% and 15%, respectively) (P<0.0001 for <1500 IU/mL *vs* higher levels).[22] The association of on-treatment HBsAg levels and sustained posttreatment response was confirmed by the NEPTUNE study,[23] where HBeAg seroconversion rates 6 months after treatment were significantly higher in patients with HBsAg <1500 IU/mL at weeks 12 and 24 (58% and 57%, respectively) compared with patients with HBsAg 1500–20000 IU/mL (42% and 35%, respectively) or patients with HBsAg >20,000 IU/mL that did not achieve sustained response and may therefore be considered for discontinuation of therapy.

In general, the serum cutoff of HBsAg predicts the intensity of a virologic response, too. Chan *et al*, reported a sustained response, that is, HBeAg seroconversion and HBV DNA ≤2000 IU/mL, occurring 12 months post–Peg-IFN treatment, being more frequently observed in patients with HBsAg ≤ 300 IU/mL at month 6 of treatment (62% *vs* 11%, P<0.001). The highest rates of response (75%) were in patients having both >1 log HBsAg decline and serum HBsAg level ≤300 IU/mL at month 6 of treatment compared with 15% in patients lacking such a combined response (P<0.001). The PPV and NPV for a sustained response by the combination of HBsAg and HBV DNA levels were 75% and 85%, respectively.[24] The association between on-therapy HBsAg levels and HBeAg seroconversion was observed in Asian patients as well.

Peg-IFN therapy of HBeAg-negative patients

In a landmark study of 48 HBeAg-negative patients receiving Peg-IFNa-2a, a decrease of 0.5 and 1 $\log_{10}$ IU/mL of serum HBsAg levels at weeks 12 and 24 of therapy had a 90% NPV and a 89% PPV for week 12 and 97% NPV and a 92% PPV for week 24 sustained response, respectively.[7] This was the first study to suggest early kinetics (week 12) of HBsAg to

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differentiate sustained responders from relapsers to Peg-IFN, although the limited sample size, the retrospective design, the heterogeneous genotype distribution, and the very strict definition of virologic response, caution against generalizability of the results. This notwithstanding, this information helps to identify early on-treatment (weeks 12 or 24) patients who are more likely to achieve a sustained response, and therefore should continue therapy up to week 48. In a retrospective analysis of HBsAg levels in the Peg-IFNa-2a registration study, patients who achieved a ≥10% decline in serum HBsAg at week 12 of treatment had a higher probability of sustained response compared with those with a lesser decline (47% *vs* 16%, $P<0.01$).[25] The association between on-treatment HBsAg decline ≥10% and sustained response in genotype D patients was analyzed in the PegBeLiver study that enrolled 96% of genotype D patients, a subgroup of patients being treated for 96 weeks. This study showed that a ≥10% decline of HBsAg at week 24 (not at week 12) of treatment, was significantly associated with a sustained response to Peg-IFN in patients treated for 96 weeks, only.[26] Early kinetics of serum HBsAg might help tailoring duration of Peg-IFN therapy to spare costs and unnecessary morbidity in nonresponders.

Among 102 HBeAg-negative patients, predominantly infected with genotype D who were treated with Peg-IFNa-2a±ribavirin for 12 months, the week 12 level of serum HBsAg and HBV DNA predicted a nonresponse. None of the 20 patients with unmodified HBsAg levels and a <2 $\log_{10}$ copies/mL HBV DNA decline, had a long-term response defined as serum HBV DNA <10,000 copies/mL and normal ALT 6 months posttreatment (100% NPV).[27] This was the first study to suggest a week 12 stopping rule for Peg-IFN treated HBeAg-negative patients, and was recently confirmed by the pooled analysis of 160 HBeAg-negative patients who received either Peg-IFN for 48/96 weeks in the phase III registration trial ($n=85$) or in the PegBeLiver study ($n=75$). The "week 12 stopping rule" performed well across these studies identifying patients who have no or a very low chance of a response, defined as HBV DNA <2000 IU/mL combined with normal ALT at 24 weeks of posttreatment followup, to either 48 or 96 weeks of Peg-IFN. However, the performance of this score was best among the 91 genotype D infected patients with 19% of patients that would be allowed to discontinue therapy, while maintaining all sustained responders on treatment. Among the 34 patients treated for 96 weeks with Peg-IFN, none of the 7 (21%) patients fulfilling the criteria the "week 12 stopping rule" achieved a response.[28]

Given the low PPV of these scores, other scores have been proposed to optimize prediction of outcome of Peg-IFN treatment. Recently, a week 24 rule has been proposed: patients with HBsAg >7500 IU/mL at week 24 had very low chance of achieving a sustained response defined as HBV DNA <2000 IU/mL 1 year posttreatment (NPV: 93% and 100% for 48 and 96 weeks treatment, respectively). If externally validated, the 24-week cutoff might be a second stopping rule for Peg-IFNα-2a treated patients, however, restricted to those infected with genotype D of HBV.[29] Indeed, there are data indicating that HBV genotype may influence the on-treatment HBsAg kinetics, thus making the identification of genotype-specific thresholds for HBsAg levels, necessary. In genotype A and B, 100% of responders to Peg-IFN (HBV DNA <2000 IU/mL 5 years posttreatment) had HBsAg ≤400 IU/mL and ≤50 IU/mL, respectively. In genotype C 41% of responders had HBsAg ≤50 IU/mL, whereas in genotype D 60% of responders had HBsAg ≤1000 IU/mL.[30]

These studies provide a rationale for stopping Peg-IFN at week 12 in approximately 20% of HBeAg-negative patients with a <2 log HBV DNA decrease and no change in HBsAg levels, since these patients would have no chances of a response even after extended therapy beyond week 48. Since this stopping-rule has not been validated for HBeAg-negative patients infected with non-D genotypes,[27-31] there is a need for genotype-specific prediction rules.

Nucleos(t)ide analogues therapy of naïve patients

Lamivudine

Patients with chronic hepatitis B treated with lamivudine (LMV) show a gradual decrease of serum HBsAg concentrations.[32] This happens, however, without obtaining HBsAg clearance, whereas an increase of HBsAg titers precedes the emergence of drug resistance. In 21 HBeAg-negative patients who were followed up for a median of 46 months, Manesis *et al*. reported a median decrease of HBsAg of 470 IU/mL (range: −64 to 2354) with a monthly rate of HBsAg decrease of 7.7 UI.[8] This was also the experience in Italy where Brunetto *et al* confirmed a modest decline of HBsAg during 48 weeks of LMV treatment of 122 HBeAg-negative patients (−0.02 $\log_{10}$ IU/mL).[6]

Telbivudine

In HBeAg-positive patients, effective therapy with telbivudine (LdT) caused progressive serum HBsAg levels decline from a baseline value of 3.8±0.6 $\log_{10}$ IU/mL to week 24 value of 3.4±0.7 $\log_{10}$ IU/mL, year 1 value of 3.3±0.8 $\log_{10}$ IU/mL and year 3 value of 3.0±1.4 $\log_{10}$ IU/mL ($P<0.0001$). During the first year, 3 patterns of HBsAg decline associated with different rates of HBsAg loss in the long-term treatment were observed: rapid (≥1 $\log_{10}$ IU/mL, mostly in genotype A) in 20% of patients, slow (0–1 $\log_{10}$ IU/mL) in 45% of patients and steady in the remaining patients. Twenty-five percent of patients with a rapid HBsAg decline achieved undetectable serum HBsAg at year 3 compared with none of the patients with steady HBsAg levels ($P=0.0024$).[33] The power of

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LdT was confirmed by a small study in 17 HBeAg-positive patients where serum HBsAg levels <2 $\log_{10}$ IU/mL at year 2 were highly predictive of sustained response, that is, HBV DNA <300 copies/mL, HBeAg seroconversion, and ALT normalization at 2 years off-treatment followup, with a 93% PPV and 100% NPV. Moreover, HBsAg decline >0.8 and >1 $\log_{10}$ IU/mL from baseline to weeks 24 and 52 of treatment were more predictive of sustained response than HBV DNA decline, having a 75% and 86% PPV and NPV, respectively, for both weeks 24 and 52 assessment.[34]

Entecavir

There is limited data on HBsAg quantification in entecavir (ETV)-treated patients. In one study, HBsAg was quantified at baseline and during ETV therapy in 33 HBeAg-positive and 37 HBeAg-negative patients, only. HBeAg-positive patients showed a mean decline of 0.38 $\log_{10}$ IU/mL at week 48, the higher decrease being observed in those who cleared HBeAg and in patients with elevated baseline ALT levels. Conversely, the HBsAg decline was negligible in HBeAg-negative patients (−0.10 $\log_{10}$ IU/mL).[35] In another small study, where 28 HBeAg-positive patients received ETV for 21 months (range: 18–24), HBsAg declined from a mean baseline value of 4.0 $\log_{10}$ IU/mL to 3.7 and 3.6 $\log_{10}$ IU/mL at months 6 and 12, respectively (P<0.001). The 5 patients with a >1 $\log_{10}$ IU/mL decline of HBsAg level from baseline to month 12 of treatment, showed a 80% cumulative incidence of HBeAg loss at 1 year compared with 30% in those with less HBsAg decline.[36]

Tenofovir

Data on HBsAg kinetics in tenofovir (TDF)-treated patients are scanty as well. In a 3-year study, HBeAg-positive patients who cleared HBsAg were those with a greater median change from baseline in HBsAg levels at week 24 compared with patients who did not (−2.41 *vs* −0.20 $\log_{10}$ IU/mL).[37] HBeAg-negative patients showed a negligible HBsAg levels decline of −0.20 $\log_{10}$ IU/mL mean reduction from baseline to year 3. HBsAg decline was quicker in patients who lost HBsAg than in those who failed to clear HBsAg at 4-year treatment.[38]

Therapy of nucleos(t)ide analogs resistant patients

Interestingly, the HBsAg decline in LMV-resistant patients in whom HBV DNA was successfully suppressed by LMV+adefovir dipivoxil (ADV) combo therapy, is suboptimal. The log decline of HBsAg levels from baseline to last observation in 39 LMV-resistant patients on LMV+ADV for 40 months (range: 24–84) was in fact <0.5 log and none of the patients cleared HBsAg.[39] More encouraging were the results of a study in Italy in 88 patients with persistently undetectable serum HBV DNA (<35 copies/mL) for at least 3 years of either LMV monotherapy (n=23) or ADV+LMV combination therapy (n=65), in whom HBsAg titers progressively declined over time with a few patients achieving HBsAg loss. The median HBsAg log titers were in fact 3.2 at year 1, 3.1 at years 2 and 3, 2.9 at year 4, and 2.8 at year 5, with an overall median decline of 0.8 $\log_{10}$ UI/mL. Twenty-one patients (27%) at 4-year and 19 (41%) at 5-year had a >1 log reduction compared with baseline and 24 (29%) patients had HBsAg levels below 250 UI/mL after 4 years of therapy. Seven (30%) long-term responders to LMV monotherapy had reduced HBsAg titers below the limit of detection (0.05 UI/mL).[40]

Overall, despite a greater suppressive effect on HBV DNA, patients on nucleos(t)ide analogs (NUC) had a slower and less pronounced HBsAg decline, even in those who later cleared HBsAg.[6,8,35] As a general rule, the HBsAg decline was less pronounced in HBeAg-negative than in HBeAg-positive patients.[35,37,38] Based on HBsAg kinetics, we estimated the time to HBsAg loss to be >10 years in LMV responders,[8] which however was extended >30 years by others.[41,42]

CONCLUSION

HBsAg is an important test that not only marks active infection with HBV, but may also predict the clinical outcome of the infection. Detection of low HBsAg and HBV DNA levels may accurately identify true inactive carriers who need neither strict followup nor antiviral treatment. Based on HBsAg quantification, a response-guided therapy in both HBeAg-positive and -negative patients treated with Peg-IFN has been developed. According to the data, therapy can be stopped at week 12 in primary nonresponders, who become candidate to alternative therapies, such as unlimited suppressive therapy with NUC. Decline of serum HBsAg may also assist NUC-treated patients, mainly the HBeAg-positive ones, however, according to slower kinetics than those related to Peg-IFN therapy. Because progressive decline of HBsAg heralds clearance of HBsAg in all instances, this may help increasing cost-effectiveness ratio of NUC therapy. New approaches to test whether Peg-IFN and NUC combination fosters HBsAg decline in long-term responders to NUC, are being explored.

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