Clinical Utility of Quantitative Hepatitis B Surface Antigen (HBsAg) in Chronic Hepatitis B Infection

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ABSTRACT

The prevalence of hepatitis B infection in Indonesia is still alarming, while its therapies cannot eradicate the virus and only aim for long term viral suppression. Hepatitis B surface antigen (HBsAg) quantification has become an emphasis on researches, regarding its capacity to identify the natural history of hepatitis B virus infection and predict the outcome of therapies. This review aims to determine the clinical role of HBsAg in chronic hepatitis B infection by reviewing textbooks, journal articles, and review articles without language restriction. This review finds that HBsAg is capable of predicting degrees of liver fibrosis severity in patients with chronic hepatitis B infection. Furthermore, HBsAg quantification can be used to distinguish inactive carriers from patients with HBeAg-negative chronic hepatitis B. The decrease of HBsAg is a good predictor of HBsAg loss, and it denotes discontinuation of nucleoside/nucleotide analog therapy. HBsAg quantification is also used in combined pegylated interferon (PEG-IFN) and nucleoside/nucleotide analog therapy. Nevertheless, this role is still controversial. Additionally, HBsAg cannot replace the major roles of hepatitis B virus deoxyribonucleic acid (HBV DNA) measurement in therapy management. Using either HBsAg or HBV DNA in therapy algorithm decreases its predictive value, hence recommendation to use both. In identifying patients with occult hepatitis B infection (OBI), HBV DNA still cannot be replaced by HBsAg quantification. Furthermore, HBsAg quantification may not be a good predictor of hepatocellular carcinoma in patients with OBI. Future studies are expected to demonstrate the role of HBsAg in current hepatitis B therapy and also future therapies.

Keywords: *quantitative HBsAg, hepatitis B virus, pegylated interferon, nucleoside/nucleotide analog, fibrosis.*

ABSTRAK

Prevalensi infeksi hepatitis B di Indonesia masih sangat tinggi, dan pilihan terapinya belum dapat menghilangkan virus dan hanya berupa supresi jangka panjang virus. Kuantifikasi hepatitis B surface antigen (HBsAg) sekarang berada pada fokus penelitian dan studi mengenai kemampuannya untuk mengidentifikasi perjalanan penyakit infeksi virus hepatitis B dan memprediksi luaran terapi. Ulasan ini bertujuan untuk membahas peran klinis HBsAg pada infeksi hepatitis B kronis, melalui pencarian buku teks, artikel jurnal, dan artikel ulasan yang diterbitkan tanpa limitasi bahasa publikasi. Hasil ulasan menemukan bahwa HBsAg dapat memprediksi derajat keparahan fibrosis liver pada penderita infeksi hepatitis B kronis dan membedakan pasien karier inaktif dari pasien dengan hepatitis B kronis dengan HBeAg negatif. Selain itu, kuantifikasi HBsAg dapat digunakan untuk membedakan karier inaktif dari pasien dengan hepatitis B kronis HBeAg negatif. Penurunan kadar HBsAg memiliki nilai prediksi bagus dalam pencapaian hilangnya HBsAg serum pada pasien dengan terapi nukleosida/

nukleotida analog. Kadar HBsAg dapat digunakan dalam algoritme terapi kombinasi pegylated interferon (PEG-IFN) dan nukleosida/nukleotida analog, walaupun studi terbaru masih menunjukkan hasil yang kontradiktif. Selain itu, HBsAg tidak dapat mengganti sebagian besar peran pengukuran HBV DNA dalam tatalaksana terapi. Hanya menggunakan salah satu dari HBsAg atau HBV DNA akan menurunkan nilai prediktif dalam algoritma terapi, sehingga disarankan untuk menggunakan keduanya. Dalam mengidentifikasi pasien dengan infeksi hepatitis B tersamar (OBI), pemeriksaan HBV DNA tidak dapat digantikan oleh kuantifikasi HBsAg. Selain itu, kuantifikasi HBsAg tidak dapat menjadi prediktor bagus terjadinya karsinoma hepatoseluler pada pasien OBI. Diharapkan studi-studi mendatang mampu membuktikan peran HBsAg dalam terapi hepatitis B yang ada sekarang maupun yang akan datang.

Kata kunci: *HBsAg kuantitatif, virus hepatitis B, pegylated interferon, nukleosida/nukleotida analog, fibrosis.*

INTRODUCTION

Hepatitis B virus is a hepatotrophic virus which is capable of causing both acute and chronic infection. The prevalence of hepatitis B infection in Indonesia is still problematic, where approximately 7.1% of Indonesian population is infected with hepatitis B.[1] Current medication of hepatitis B still aims for long-term suppression of viral infection; therefore increasing life the quality of life of infected patients.[2]

Currently accepted therapies have not been able to eradicate the virus but only manage to suppress its replication, hence inevitable risk of cirrhosis and hepatocellular carcinoma. Treatment with interferon is thought to be more beneficial in reaching ideal target of therapy (defined by hepatitis B surface antigen/HBsAg loss with or without anti-HBs seroconversion).[2,3] As previously mentioned, HBsAg level can reflect intrahepatic cccDNA activity, so HBsAg quantification can be used to observe patient's response to therapy.

HBsAg quantification has been discovered since 20 years ago, but its measurement is still widely performed because of multiple benefits. HBsAg is crucial in determining choice of therapy, when to begin therapy, success rate of therapy, and when to cease therapy of patients with hepatitis B infection ("therapy" refers to one of hepatitis B antiviral therapies). Moreover, HBsAg is believed to be able to predict liver condition during course of hepatitis B infection, and thus it is likely to predict the degree of progressing inflammation/fibrosis of the liver, and predict the impact done by the inflammation and fibrosis, such as hepatocellular carcinoma.[2,4] This article aims to discuss clinical role of HBsAg quantification comprehensively, especially its role in Asia.

HEPATITIS B SURFACE ANTIGEN (HBSAG) IN HEPATITIS B VIRAL COURSE OF INFECTION

Hepatitis B's course of infection comprises of: immune tolerant phase, immune clearance phase (HBeAg-positive chronic hepatitis), inactive carrier phase, reactivation phase (HBeAg-negative chronic hepatitis).[2] Chronic hepatitis B (CHB) can be divided

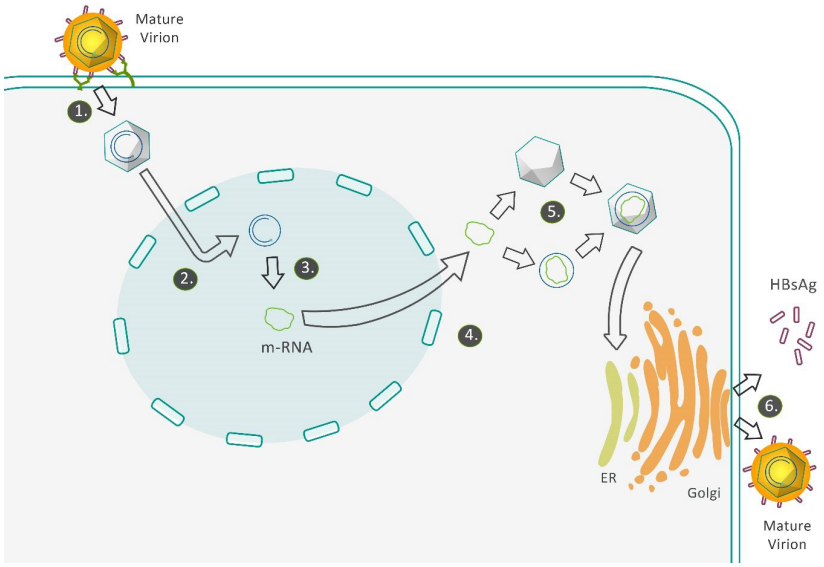

Figure 1. Illustration of life cycle of hepatitis B virus. (1) Mature virion enters the cytoplasma of a host hepatocyte, (2) hepatitis B DNA is released from its subviral particles and cccDNA is created, (3) mRNA is formed by the nuclear reservoir of cccDNA, (4) mRNA translocation into cytoplasm, (5) translational pathways, and (6) HBsAg and virion secretory pathways[5]

into two major forms, hepatitis B virus *e* antigen (HBeAg) positive and HBeAg negative. At immune tolerant phase, the patients usually have HBeAg-positive virus in their serum, high HBV DNA level, and normal range of alanine aminotransferase (ALT) level. The following phase (immune clearance) is a phase that induces HBeAg seroconversion.[4] HBsAg is an envelope protein of hepatitis B virus whose level is known to reflect intrahepatic cccDNA activity.[5] As shown by figure 1, hepatitis B virus infecting hepatocytes locate its cccDNA into the host's nucleus and starts transcription to form mRNA. The mRNA will be a template for structural protein translation (envelope, i.e. HBsAg) and reverse transcriptase enzyme. The mRNA then undergoes reverse transcription into DNA that will be integrated to structural protein formed intracellularly. Hyperactivity of intrahepatic cccDNA will trigger excessive HBsAg translation and will be secreted along mature virion into the patient's blood. Therefore, quantitative HBsAg is needed to determine the hepatitis B virus's course of infection.

ROLE OF QUANTITATIVE HEPATITIS B SURFACE ANTIGEN (HBSAG) AS PREDICTOR OF LIVER FIBROSIS SEVERITY

A research by Goyal et al showed that HBsAg level inversely correlates with degree of liver fibrosis severity in HBeAg-positive chronic hepatitis B patients. The lower the level of HBsAg in HBeAg-positive chronic hepatitis B patients, the more critical the progress of liver fibrosis in the patients.[6] This happens because HBsAg level in the serum varies in accordance with the host's phase of infection, where the highest level of HBsAg is found in immunotolerant patients, while the lowest level of HBsAg is found in inactive carriers. Other studies concluded that serum HBsAg level ≥ 25,000 IU/mL and normal ALT (≤ 2 times of upper limit of normal) have sensitivity of 86.4%, specificity of 75%, and positive predictive value of 92.7% to predict low-grade fibrosis (≤ F1).[7] This result is an almost perfect predictor for degree of liver fibrosis severity in chronic hepatitis B patients.

ROLE OF QUANTITATIVE HEPATITIS B SURFACE ANTIGEN (HBSAG) IN IDENTIFYING THE RISK OF REACTIVATION IN INACTIVE CARRIERS

The diagnostic criteria of inactive carrier used in Indonesia are as following: (1) seropositive HBsAg > 6 months; (2) HBeAg negative; (3) serum ALT in normal value; (4) HBV DNA level < 2,000 IU/mL; (5) liver biopsy not showing dominant inflammation.[2,3,8] The measurement of quantitative HBsAg is focused on identifying inactive carriers with high reactivation risk, where they may be used as a suitable therapy indication. A study by Martinot-Peignoux et al (2013), HBsAg level ≥ 1,000 IU/mL and HBV DNA ≥ 200 IU/mL may be used to identify inactive carriers with high risk of reactivation (this limit has NPV of 96% and sensitivity of 92%).[9] This finding indicates essential role of quantitative HBsAg in selecting inactive carriers who need initiation of therapy.

ROLE OF QUANTITATIVE HBSAG IN PREDICTING OUTCOME OF PEGYLATED INTERFERON THERAPY

Therapy with pegylated interferon (PEG-IFN) aims to reach immunological control and HBsAg clearance after therapy; therefore PEG-IFN medication is prescribed in limited duration, usually only for 48 weeks.[9] Decline in HBsAg is associated with preceding immune response activation, reflected by increase of serum ALT and IFN gamma inducible protein 10 (IP-10, CXCL-10) levels. Additionally, change of serum HBsAg level during PEG- IFN therapy reflects adjustment of intrahepatic cccDNA and HBsAg situation, and thus the decline in serum HBsAg level is associated with effective immune response induction of anti HBV.[5] Patients' HBeAg status is important in therapy algorithm and its prognosis, so the role of quantification and its interpretation among patients with HBeAg-positive and HBeAg-negative hepatitis B infection is very dissimilar.

Hepatitis B e-antigen (HBeAg)-positive

Criteria of starting therapy for patients with HBeAg-positive/negative hepatitis B in Indonesia have yet to include quantitative HBsAg. According to National Consensus of Hepatitis B Management in Indonesia in 2017, the criteria for HBeAg-positive patients consist of: (1) HBV DNA level > 2 x 10^4 IU/mL with normal ALT level or 1-2x upper limit of normal; (2) HBV DNA level > 2 x 10^4 IU/mL with ALT level > 2x upper limit of normal, and HBV DNA level < 2 x 10^4 IU/mL regardless of ALT level.[2] On the first condition, the patient is observed every 3 months and therapy will not be started unless moderate or severe degree of inflammation or significant fibrosis is found. On the second condition, therapy can be started after 3-month observation, and no seroconversion is apparent while ALT level persists in > 2x upper limit of normal during

said 3-month observation (regardless of inflammation degree or severe fibrosis finding). On the third condition, therapy is started if there is moderate until severe degree of inflammation or significant fibrosis in 3-month observation.

It has been known that HBeAg-positive patients have a higher mortality rate than HBeAg-negative patients, but they are more responsive on therapy than those with negative HBeAg.[2,9] Identification of HBeAg-positive patients with criteria that possess high sensitivity and specificity have been proposed by several researchers. High but stable HBsAg (~5 $\log_{10}$ IU/mL) and serum HBV DNA level (> 8 $\log_{10}$ IU/mL) are distinctive marker of immune tolerant phase in HBeAg-positive patients in Asia.[10] HBsAg seroconversion is also needed to be assessed in the patients because one of the means of observing hepatitis B improvement is from HBsAg seroconversion. Studies by Chan et al concluded that quantitative HBsAg cannot predict sudden HBsAg seroconversion, and its decline rate is very slow.[10] Those findings show that HBsAg level cannot be used to follow up HBeAg seroconversion progression in early phase, while HBV DNA level remains the best predictor for HBsAg loss. Although, Martinot-Peignoux et al summarized that quantitative HBsAg in one year has a good predictive value to interpret HBsAg decline. HBsAg loss is indicated by decrease ≥ 1 $\log_{10}$ IU/mL or single measurement below 200 IU/mL. High probability for HBsAg loss is a decrease of HBsAg ≥ 0.3 $\log_{10}$ IU/mL/year.[9]

Quantitative HBsAg is known to have an important role as a marker during PEG-IFN therapy in HBeAg-positive patients to reach sustained virological response (SVR). As per criteria established by the National Consensus of Hepatitis B Management in Indonesia in 2017, HBeAg-positive patients are said to be responders if there is decline in HBV DNA > 2 log at week 12 and quantitative HBsAg level < 1,500 IU/mL at week 12 and week 24. HBeAg- positive patients are said to be nonresponders if there is decline in HBV DNA < 2 log at week 12 and/or HBsAg level > 20,000 IU/mL at week 12 and 24.[2] the rate of HBeAg seroconverion is higher in patients with HBsAg level ≤ 1,500 IU/mL at week 12 of PEG-IFN therapy, with positive predictive value of 57% and negative predictive value of 72%.[9] Alternatively, patients with high level of HBsAg (> 20,000 IU/mL) at week 24 has a very low probability of therapy success.[4] Patients with positive HBeAg show SVR 25-30% with PEG-IFN therapy, where SVR value is higher than HBeAg-negative patients (25%).[9]

Aforementioned findings show that quantitative HBsAg amends and improves chronic hepatitis B management with IFN therapy. Cease of IFN therapy after 12 weeks can be determined by HBsAg quantifications, where algorithm of therapy success can be observed just by quantitative HBsAg without quantitative HBV DNA. In HBeAg-positive patients, PEG-IFN therapy can be stopped at week 12 if HBsAg fails to decline more than the test's standard error or if HBsAg level is > 20,000 IU/mL. Martinot-Peignoux et al (2014) also concluded that at week 24, PEG-IFN therapy is ceased in all patients with HBsAg level > 20,000 IU/mL, regardless of infecting hepatitis B genotype.[9]

Hepatitis B e-antigen (HBeAg)-negative

Different from illnesses caused by positive HBeAg, patients with HBeAg-negative HBV reach decline in HBV DNA to the point of undetectable during therapy, but may relapse after therapy is finished or ceased[11] the only quantifiable serology during PEG-IFN therapy is HBsAg. Therefore, the measurement of HBsAg in patients with negative HBeAg is essential because HBsAg level is the only quantifiable marker during therapy-induced HBV DNA suppression.

Conditions for HBeAg-negative patients determined by National Consensus of Hepatitis B Management in Indonesia in 2017 are: (1) HBV DNA level > 2 x 10^3 IU/mL with ALT level >2x upper limit of normal; (2) HBV DNA > 2 x 10^3 IU/mL with normal ALT level or 1-2x upper limit of normal; (3) HBV DNA level < 2 x 10^3 IU/mL with ALT level beyond normal value; (4) HBV DNA < 2 x 10^3 IU/mL with normal consistent ALT level. In criterion (1), therapy is started if there is no seroconversion within 3 month observation. In criteria (2), (3), and (4), therapy is initiated after moderate until severe inflammation, or significant liver fibrosis is evident. The patient is declared a responder if there is decline in HBV DNA > 2 log at week 12 and HBsAg level > 10% from baseline at week 12 and week 24. The patient is declared nonresponder if there is decline in HBV DNA < 2 log at week 12 and/or no decline in HBsAg level from baseline at week 12 and week 24.[2]

Resembling HBeAg-positive patients, HBeAg-negative patients showing sharp decline in HBsAg level during therapy are easier to reach SVR. Serum HBsAg decline ≥ 0.5 log IU/mL at week 12 has a positive predictive value of 89% for SVR. Absence of HBsAg decline ≥ 1 $\log_{10}$ IU/mL at week 24 has a negative predictive value of 92% for non-SVR. Absence of HBsAg decline and HBV DNA decline < 2 $\log_{10}$

IU/mL has an SVR with negative predictive value of 100%. SVR with high predictive value after 48 weeks of therapy, and HBsAg loss from serum 3 years after cease of therapy are seen in patients who, during therapy, experience HBsAg decline ≥ 1 $\log_{10}$ IU/mL with HBsAg level < 10 IU/mL at the end of therapy.[9]

A study by Rijckborst et al showed that HBV DNA level is also needed in addition to HBsAg level to predict response. When using both serum markers, the therapy prediction will improve, compared with using only either marker.[11] The study result concluded that if a patient fails to reach HBsAg decline at week 12, and fails to reach HBV DNA decline > 2 log IU/mL, the patient will never reach SVR (defined as HBV DNA level < 2,000 IU/mL with normal ALT level at 6 months after cease of therapy). This is commonly known as 12 week rule and has a negative predictive value of 100%.[5,9,11]

ROLE OF QUANTITATIVE HEPATITIS B SURFACE ANTIGEN (HBSAG) IN PREDICTING OUTCOME OF NUCLEOSIDE/NUCLEOTIDE ANALOG THERAPY

The goal of hepatitis B therapy with nucleoside/nucleotide analogs is to maintain hepatitis B viral suppression during therapy. Nucleoside/nucleotide analogs should be given indefinitely because cease of medication triggers viral reactivation.[9] Long-term viral suppression may improve liver histology and may even reverse cirrhosis in 5 year period of therapy.[12] During therapy, HBV DNA will quickly decrease and become undetectable, but as pointed out by several studies, HBsAg decline during therapy with nucleoside/nucleotide analogs is less seen, compared with that during therapy with PEG-IFN.[13] Although mechanism of HBsAg decline during nucleoside/nucleotide analog therapy is still unknown, it can reflect degree of host's immunity against the virus and the decrease in cccDNA in hepatocytes.[3] Several theory declares that HBsAg decline is lower during nucleoside/nucleotide analog therapy compared with PEG-IFN therapy may be caused by nucleoside/nucleotide analog mechanism that affects reverse transcription of pregenomic RNA, but does not affect cccDNA and subgenomic RNA, whose translational activities are associated with HBsAg level.[5] Therapy with nucleoside/nucleotide analogs should be continued before the condition meets indication of therapy cessation or signs of resistance or failure of therapy. At the end of therapy, HBsAg quantification (or anti-HBs if HBsAg is undetectable) is done. Cessation of hepatitis B therapy with nucleoside/nucleotide analogs in Indonesia adheres to HBeAg status and the patient's cirrhosis status.[2]

HBeAg-positive

Principle of nucleoside/nucleotide analog therapy cessation for HBeAg-positive patients in Indonesia does not apply quantitative HBsAg. Referring to National Consensus of Hepatitis B Management in Indonesia (2017), HBeAg-positive patients without cirrhosis can terminate nucleoside/nucleotide analog therapy after persistent ALT level, HBeAg seroconversion, and undetectable HBV DNA is evident for minimum of 1 year.[2] Median duration needed for HBeAg-positive patients using nucleoside/nucleotide analogs to deplete HBsAg from serum is 36 years.[14]

Other research shows that in general, patients undergoing therapy with nucleoside/nucleotide analogs need median of 52.2 years to deplete HBsAg from serum.[4] Recommendation of nucleoside/nucleotide analog therapy cessation by Consensus of Hepatitis B Management in Indonesia in 2017 is to use the rule of HBeAg seroconversion with undetectable HBV DNA in serum, maintained for 12 months (in patients without cirrhosis). In HBeAg-positive patients with cirrhosis and achieving HBeAg seroconversion, therapy is recommended to be continued indefinitely.[2]

Besides determining when to stop nucleoside/nucleotide analog therapy, quantitative HBsAg can be used to predict SVR in HBeAg-positive patients using nucleoside/nucleotide analogs. HBsAg level < 100 IU/mL is known to be predictive for SVR 2 years after the end of therapy. Patients showing HBsAg level during therapy ≤ 3 $\log_{10}$ IU/mL demonstrate higher relapse (31% patients) than patients with HBsAg level ≤ 2 $\log_{10}$ IU/mL (9% patients).[15] Currently, there is no official HBsAg level cutoff to be used in therapy cessation criteria. However, several studies have concluded several cutoff variations that are open for further discussion and research. HBsAg level cutoff below 2-3 $\log_{10}$ IU/mL can be used in therapy cessation criteria, as summarized by Liang et al.[16]

Hepatitis B e-antigen (HBeAg)-negative

There have not been criteria to cease nucleoside/nucleotide analog therapy in patients with negative HBeAg in Indonesia because ending therapy (especially in patients with cirrhotic complications) increases risk of decompensated cirrhosis and death.[2] A study declares that nucleoside/nucleotide analog therapy can be stopped after HBsAg is lost in serum. Study by Zoutendijk et al concluded that median duration needed by HBeAg- negative patients with nucleoside/nucleotide analog therapy to reach HBsAg los in

serum is 39 years.[14] The study, however, only employ patients using entecavir or tenofovir as samples because both drugs are currently known to be the most potent nucleoside/nucleotide analogs, for that reason this review does not elaborate another nucleoside/nucleotide analogs.[2] Using entecavir (nucleoside) and tenofovir (nucleotide), 8 year therapy is needed (median) to reach HBsAg decline as much as 1 $\log_{10}$ IU/mL from baseline and reach HBsAg clearance.[14] Still, in study by Reijnders et al (2011), in patients receiving either PEG-IFN or ETV for 48 weeks, HBsAg decline is only seen in HBeAg-positive patients after 48 week therapy with entecavir. There is no HBsAg decline in HBeAg- negative patients receiving entecavir.[13] Recommendation by National Consensus of Hepatitis B Management in Indonesia in 2017 for nucleoside/nucleotide therapy cessation in HBeAg-negative patients without cirrhosis is when the patient reaches HBsAg loss. In HBeAg-negative patients with cirrhosis, therapy should be continued indefinitely.[2]

Quantitative HBsAg can also be used to predict response of nucleoside/nucleotide analog therapy. Research by Seto et al stated that the best indicator for HBsAg seroclearance is baseline HBsAg level < 1,000 IU/mL and HBsAg decline rate ≥ 0.166 $\log_{10}$/IU/mL/year. Baseline HBsAg level < 1000 IU/mL indicator has a negative predictive value of 98% and positive predictive value of 38%, while HBsAg decline ≥ 0.166 $\log_{10}$/IU/mL/year indicator has a negative predictive value of 98% and positive predictive value of 26%.[17] The same researchers also proved that HBsAg level decline after tenofovir therapy is bigger in patients having baseline of ≥ 3 $\log_{10}$ IU/mL compared with those with baseline < 3 $\log_{10}$ IU/mL. In baseline < 3 $\log_{10}$ IU/mL, HBsAg level remains the same/stable.[17] These findings indicate that quantitative HBsAg has a potential to be a standard of SVR prediction by baseline HBsAg quantification and HBsAg decline quantification in yearly basis.

ROLE OF QUANTITATIVE HEPATITIS B SURFACE ANTIGEN (HBSAG) IN PREDICTING OUTCOME OF THERAPY WITH COMBINED PEGYLATED INTERFERON AND NUCLEOSIDE/NUCLEOTIDE ANALOG

The effect of combination of PEG-IFN and nucleoside/nucleotide analogs on hepatitis B patients is still controversial. A study by Chan et al showed that in HBeAg-positive patients, therapy with just PEG-IFN gives more significant HBsAg decline compared with combined therapy of PEG-IFN and lamivudine/adefovir/tenofovir. Meanwhile in HBeAg-negative patients, combined therapy of PEG-IFN and nucleoside/nucleotide analogs gives significantly greater HBsAg decline compared with therapy with either PEG-IFN or nucleoside/nucleotide analogs.[18]

Quantitative HBsAg can be used to predict serum HBsAg loss in combined therapy of PEG-IFN and nucleoside/nucleotide analogs. A study by Takkenberg et al summarized that HBsAg cutoff of 20 IU/mL at week 24 after therapy is a highly predictive indicator for serum HBsAg loss at week 144. This indicator has a positive predictive value of 89% and negative predictive value of 100%.[19]

ROLE OF QUANTITATIVE HBSAG TO SUBSTITUTE QUANTITATIVE HBV DNA

Role as a Viral Marker

Compared with quantitative HBV DNA or intrahepatic cccDNA, HBsAg quantification has its perks in cost, convenience, and presence of automatic quantifiers. cccDNA reflects damage on infected hepatocytes, and the most common measuring method is liver biopsy. On the other hand, quantitative HBV DNA prompts high cost and lengthy period. Therefore, quantitative HBsAg proves to be an interesting value as a substitute for intrahepatic cccDNA measurement or serum HBV DNA level. Several studies show that quantitative HBsAg is associated with intrahepatic cccDNA level.[43] However, study by Lesmana et al in Jakarta, Indonesia declared that production of subviral particles (SVP) (shown by HBsAg level) is not significantly different between HBeAg- positive and HBeAg-negative patients. Additionally, there is low correlation between serum quantitative HBsAg and pregenomic RNA (pgRNA), replicative activity (indicated by pgRNA/cccDNA), and virion productivity (relaxed circular DNA/cccDNA). Viral load, quantitative serum HBsAg level, and all of HBV intrahepatic markers (total DNA, pgRNA, cccDNA, rcDNA) are significantly higher in HBeAg-positive patients.[20] Lesmana et al concluded that HBeAg-positive patients may have higher intrahepatic and serum virion and marker production, but the replicative activity and production of subviral particles are still at the same rate with HBeAg- negative patients.[20] Conversely, a study by Primadharsini et al in Denpasar, Indonesia reported that there is significant correlation between serum quantitative HBsAg and HBV DNA. Quantitative HBsAg correlates significantly with HBV

DNA in HBeAg-positive subgroup (r = 0.717; p = 0.000). Significant correlation is also found in HBeAg-negative subgroup (r = 0.443; p = 0.006), although the correlation is weak.[21] The latter study from Indonesia points out that quantitative HBsAg can be considered as an aid, if not an alternative to quantitative HBV DNA as a viral marker, and further studies are needed to determine HBsAg application in all patients with chronic hepatitis B in Asia.

Function to Identify Occult Hepatitis B Virus Infection

Occult hepatitis B virus infection (OBI) is one of clinical spectra in hepatitis B infection where there is HBV DNA without detectable HBsAg.[2] OBI prevalence is various, from only 1% up to 87%. OBI may present with two forms: seropositive and seronegative OBI. In seropositive OBI, HBV DNA level is detected in serum with positive anti-HBc and anti-HBs, or only positive anti-HBc. In seronegative OBI, HBV DNA level is detected in the serum and/or liver biopsy but neither anti-HBs nor anti-HBc is detectable. Pathogenesis of OBI is still unknown. Diagnosis of OBI may have clinical means in which: (1) infection is transmitted through blood transfusion, hemodialysis, organ transplantation, and vertically; (2) infection may trigger hepatitis B viral reactivation; (3) OBI contributes to chronic liver disease; (4) OBI increases risk of hepatocellular carcinoma.[22] Thus, diagnosing OBI is one of the roles of quantitative HBV DNA that cannot be substituted by quantitative HBsAg.

ROLE OF QUANTITATIVE HEPATITIS B SURFACE ANTIGEN (HBSAG) TO PREDICT HEPATOCELLULAR CARCINOMA

Quantitative HBsAg as one of predictors of hepatocellular carcinoma is still controversial. A study by Tseng et al, in HBeAg-positive patients already forming hepatocellular carcinoma, baseline value of HBsAg and HBV DNA can be used as one of the predictor. On the other hand, in HBeAg-negative patients with low viral load, the risk of hepatocellular carcinoma can be predicted from HBsAg level, age, and ALA (δ - aminolevulinic acid) level, where there is increase in risk in patients with high ALA and HBsAg level (≥ 1,000 IU/mL) and in elderly patients.[23]

However, study by Kwak et al showed that there may be hepatitis B infection without detectable HBsAg in serum. The decline of HBsAg serum may be found in following conditions: (1) occurrence of OBI; (2) there is occult hepatitis B infection after resolution from acute hepatitis B infection; (3) decline in serum HBsAg level because of progressive decline in HBV replication.[24] This finding indicates that there may be persistent hepatitis B infection in hepatocellular carcinoma patients with negative HBsAg but with positive HBV DNA. Histopathology from hepatocellular carcinoma in patients with negative HBsAg usually mimics normal liver imaging, where there is no cirrhotic characteristic in the patients. This finding shows that quantitative HBsAg is not a good predictor for hepatocellular carcinoma in patients with OBI.

CONCLUSION

Quantitative HBsAg has an important role in identifying hepatitis B patient's course of disease and its risk of complication. Measuring method and cost are several reasons of why HBsAg is an ideal indicator in chronic hepatitis B management, although several functions of HBV DNA cannot be replaced by HBsAg, seen in its use in therapy algorithm, and identification of patients with occult hepatitis B infection (OBI). In therapy algorithm, using only either HBsAg or HBV DNA reduces the effectivity of the algorithm. Although, several studies show that quantitative HBsAg alone has a high predictive value in detecting the outcome of PEG-IFN and nucleoside/nucleotide analog therapy, and therefore further studies are necessary to determine the role of quantitative HBsAg to be used as a future guideline of therapy of hepatitis B in Asia.

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