Growing attention to an old marker, hepatitis B surface antigen, in the natural history of chronic hepatitis B

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Abbreviations: HBsAg, Hepatitis B surface antigen; HBV, hepatitis B virus; cccDNA, covalently closed circular DNA

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Serum hepatitis B surface antigen and hepatitis B e antigen titers: disease phase influences correlation with viral load and intrahepatic hepatitis B virus markers.

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Hepatitis B surface antigen (HBsAg), originally referred to as “Australia antigen” was discovered approximately 40 years ago. Over the years, the presence of this antigen has remained the hallmark of hepatitis B virus (HBV) infection. HBsAg is the viral envelope and is composed by 3 proteins, such as S (small, S domains), M (medium, preS2+S) and L (large, preS1+preS2+S) codified by only one open reading frame. The S-HBs protein is the major component of the virion envelope and the subviral HBsAg particles, such as filaments and spheres, while virions and filaments contain more M-HBs, and in particular, more L-HBs proteins than spheres.1,2 In infected individuals, subviral particles are present in at least 100-fold excess over virions.3 The processing of production and secretion of HBsAg is complex, and the comparative proportion of each S-, M-, L-HBsAg component in the serum and liver varies according to the state of HBV replication.4

The recent growing interest in quantitative analysis of HBsAg as a clinical parameter has been based on several studies that observed its relationship with serum and liver HBV DNA.5,7 In fact, quantification of HBsAg was introduced more than 20 years ago, but its clinical usefulness has been questioned due to the lack of appropriate standardization.8 Consequently, HBsAg has long been used typically as a qualitative marker for diagnosing an ongoing HBV infection. Recently, a quantitative, fully automated chemiluminescent microparticle immunoassay for the detection of HBsAg became available and offered more reliable quantitative data for HBsAg at a wide range of concentrations.5 It has been suggested that serum HBsAg levels correlate well with intrahepatic amounts of total HBV DNA and covalently closed circular DNA (cccDNA), which is responsible for viral persistence.6,7 Furthermore, reduction in HBsAg serum levels reportedly provided good predictive ability in patients treated with antiviral therapy. In HBeAg-negative individuals, serum HBsAg levels <10 IU/mL at week 48 and on-treatment decline >1 log IU/mL have been significantly associated with sustained HBsAg clearance 3 years after treatment, while a decrease of 0.5 log IU/mL and 1 log IU/mL in HBsAg levels at weeks 12 and 24 of therapy, respectively, have high predictive values of a sustained virologic response.9,10 Although these results suggest the potential clinical usefulness of quantitative HBsAg as an on-treatment predictor, such a good correlation was only observed in the setting of immunomodulatory agents (pegylated interferon therapy).9,10 Thus, whether or not HBsAg serum levels are still efficient as a marker for on-treatment prediction for
response to oral nucleos(t)ide analogues remains to be determined in future studies.

The significance of HBsAg levels in the natural course of HBV infection is another key issue in need of detailed evaluation. In fact, HBV replication and HBsAg/HBV-DNA production go through a complex process, which accompanies highly dynamic changes during the long-lasting interaction between virus and host immunity. More recently, the role of quantification of serum HBsAg has been explored in a subset of European and Asian HBV-infected cohorts. The overall correlation between HBsAg and HBV DNA levels was noted in both study populations. However, when it was analyzed separately by different phases of chronic HBV infection or by HBV genotypes, the correlation was shown to become weak or negligible. More specifically, a positive correlation between serum HBsAg and HBV DNA levels was only observed in the early phases of infection, but disappeared in the late phases (HBeAg-negative status). Indeed, the correlation was totally absent for patients with HBV genotype A.

The direct link between HBsAg and HBV DNA levels is an intriguing issue. Theoretically, the levels of the virion and HBsAg production would be correlated, if a potent host immune targets concordantly both virion and HBsAg synthesis processes, leading to the effective control of HBV replication. However, the immune target of host against viral replication versus HBsAg pathways may not remain in continued concordance through the natural course of infection. As noted in relevant studies, the HBsAg/HBV DNA ratios are significantly higher in the low replicative phase than other phases of infection, irrespective of study population. This may suggest that subviral particles are produced far in excess of virions, with altered production of HBsAg between its three components of L, M, and S proteins, in this subset of patients. Thus, the relationships between HBsAg and HBV DNA levels should be understood in light of the predominant pathway of HBsAg production versus viral replication in the course of chronic HBV infection.

It is well known that nearly all (>95%) chronic HBV carriers in Korea have genotype C, which is associated with a high prevalence of basal core promoter mutants, even before HBeAg seroconversion. In this context, it needs to be determined how serum HBsAg concentration functions in the natural history of HBV infection within the same category of genotype C associated with particular viral variants among the Korean population. Recent Korean studies involving a large number of antiviral-naïve patients at various disease stages of hepatitis B have shown varying clinical significance of HBsAg levels according to the disease phases. Cross-sectional studies in Korea by Yoo et al. and Kim et al. yielded similar findings regarding HBsAg levels related to the natural course of HBV infection (Table 1). In agreement with the previous European and Asian cohort studies, HBsAg levels in the two Korean studies were highest at 4.1-4.2 log IU/mL in the immune tolerant phase and lowest at 2.3-3.1 log IU/mL in the low replicative phase during the course of HBV infection. The overall relationship between serum HBsAg and HBV DNA levels was modest (r=0.383-0.700). With a stratified analysis by HBeAg status, there was a tendency for a better correlation between HBsAg and HBV DNA in HBeAg-positive patients (r=0.463-0.706), as compared to HBeAg-negative patients (r=0.064-0.521). In both studies, age was consistently identified to be negatively correlated with serum HBsAg levels, indicating that production of HBsAg proteins gradually decreases with age, under effective immune control of HBV replication and HBsAg synthesis. One of the important concerns in studies involving the natural history of HBV is the fact that the classification of disease stage in HBV carriers is not always certain, and rather, many individuals are indeed on the border between different stages of HBV infection. Given that liver biopsies are not routinely performed in all patients, the current categorizing system depending on a single time point measurement of HBeAg and HBV DNA can potentially result in the misdiagnosis of a disease stage, because of the highly fluctuating nature of serum HBV DNA levels in each patient. For this reason, it is highly likely that multiple serial measurements of virologic markers rather than reliance on only a single measurement may improve the acceptance of its value to...