HBsAg Quantification to Predict Natural History and Treatment Outcome in Chronic Hepatitis B Patients

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KEYWORDS

• Personalized medicine • Prediction • PEG-IFN • Analogues • HBV tools • Prognosis

KEY POINTS

- Serum hepatitis B surface antigen (HBsAg) level reflects the transcriptional activity of the covalently closed circular DNA in the liver.
- In hepatitis B e antigen (HBeAg)–positive chronic hepatitis B, HBsAg level is higher in the immune tolerance phase than the immune clearance phase.
- In HBeAg negative patients, combination of low hepatitis B virus (HBV) DNA and low HBsAg levels may predict inactive carrier status, low risk of hepatocellular carcinoma, and probability of HBsAg loss.
- HBsAg surrogate marker to predict peginterferon therapy outcome.
  - Absence of decline at week 12: prediction of non-response "stop therapy".
  - Any decline at week 24: prediction of response "continue therapy" 48 weeks.
- Although the HBsAg decline is slow with nucleos(t)ide analogue therapy, a rapid decline may predict future HBsAg seroclearance.

WHY QUANTIFY HEPATITIS B SURFACE ANTIGEN IN 2013

At baseline identification of

Inactive carriers
Severity of the liver disease
Probability of hepatocellular carcinoma (HCC)
Probability of hepatitis B surface antigen (HBsAg) loss

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Clin Liver Dis 17 (2013) 399–412
http://dx.doi.org/10.1016/j.cld.2013.05.006 **liver.theclinics.com**
1089-3261/13/$ – see front matter

HBsAg on treatment kinetics prediction of treatment outcome:

Pegylated interferon: stopping rule
Increase treatment duration?
NUCs: stopping rule in hepatitis B e antigen (HBeAg)–positive patients?
identification of patients with high probability of HBsAg loss.

The hepatitis B virus (HBV) is a small DNA virus. On entry into the cell, HBV sheds its protein coat, and the partially double-strand genome is transported into the nucleus of the hepatocyte, where it is transformed into a fully double-strand covalently closed circular DNA (cccDNA). The cccDNA resides in the nucleus of infected hepatocytes, where it acts as a template for transcription of the viral gene and recycles in the nucleus to renew the cccDNA pool.[1,2] Viral proteins of clinical importance include the envelope protein (HBsAg) whose synthesis during the HBV viral life cycle is complex. HBsAg production exceeds that required for virion assembly, and excess surface envelope proteins are covalently linked and secreted as empty non-infectious filamentous or spherical sub-viral particles.[3] These empty particles may co-exist with anti-HBs as part of circulating immune complexes.[4] Serum HBsAg is a result of the combination of these proteins (complete virion, filamentous or spherical sub-viral particles). HBsAg quantification measures all 3 forms of systemic HBsAg.

Several studies have shown the relationship between intrahepatic markers of HBV infection (cccDNA and integrated HVB DNA) and serum HBsAg.[3,5–7] Differences in HBsAg levels during the different phases of the disease reflect the distribution of cccDNA during the respective infection phases. HBsAg levels are higher in HBeAg positive (+) than in HBeAg negative (−) patients.[6–8]

CLINICAL APPLICATIONS

HBsAg seroconversion (loss of HBsAg and development of anti-HBs) is rarely observed during the natural course of chronic HBV infection. The annual incidence is 1% to 2% worldwide.[1] It is the ultimate goal of therapy. Recently, quantitative serum HBsAg assays have been developed,[9,10] and the importance of HBsAg quantification has been recognized as an important marker to monitor the natural history in chronic hepatitis and predict treatment outcome.[11–13] HBsAg levels decrease more in patients receiving interferon (IFN), an immune modulator, than in those receiving nucleos(t)ides analogues (NA), potent inhibitors of HBV DNA replication.[14]

HBSAG QUANTIFICATION

Several fully automated assays are commercially available. The assays most frequently used in Europe are the Cobas e411 HBsAg II assay (Roche Diagnostics GmbH Mannheim, Germany), the Architect HBsAg QT assay (Abbott, Chicago, IL USA), the ETI-MAK-1 assay (Diasorin, Turin Italy), and the Monolisa HBsAg ultra assay (Bio-Rad Laboratories Redmond, WA, USA). Results observed with both assays a very well correlated and closely in agreement across all HBV genotypes.

Studies have shown that serum HBsAg levels vary according to the different phases of HBV chronic infection. These observations emphasize that serum HBsAg levels reflect the interplay between the virus and the immune system providing complementary information on viral load. The interest in HBsAg quantification started with the possible observation of its association with the level of covalently closed circular (ccc) DNA, the template for viral replication inside the nuclei of hepatocytes. HBsAg has been shown to be a surrogate marker for cccDNA. Werlé–Lapostolle and colleagues[3] report a significant decrease in cccDNA and serum HBsAg and HBV