Hepatitis B Surface Antigen Quantification as a Current-Day Paradox: Obtaining the Gold in the Face of Diminishing Returns

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Major advances have been made in the treatment of hepatitis B during the past 5 years. However, much remains to be accomplished because current drug therapy does not eradicate infection. As a result, virologic responses are not always durable and hepatitis B surface antigen (HBsAg) generally remains positive. The management of hepatitis B e antigen (HBeAg)-negative hepatitis B remains particularly problematic because this disorder is associated with high rates of virologic relapse after interferon or several years of nucleoside analogue treatment.[1] The latter observation has led to the belief that continuous viral suppression is generally necessary and HBsAg clearance is the most reliable treatment endpoint.[2]

HBsAg clearance comes as close to a clinical cure of disease as one can expect to achieve in hepatitis B. Support for this comes from natural history studies demonstrating increased length of survival, lower rates of hepatic decompensation, and reduction in the frequency of hepatocellular carcinoma in patients with cirrhosis who clear HBsAg.[3] Molecular studies using real-time polymerase chain reaction (PCR) have shown extremely low levels of covalently closed circular DNA (0.002 copies/hepatocyte) in patients who have cleared HBsAg.[4] This in turn explains the reduced risk of reactivated hepatitis B when anti-HBc–positive/HBsAg-negative patients are treated with chemotherapy for malignancy.[5]

Despite the added clinical importance of HBsAg clearance, however, this event has not been included as a primary endpoint in treatment trials because of the low frequency of its occurrence. The majority of nucleoside analogue studies, even with prolonged therapy, have demonstrated rates of HBsAg clearance comparable to those observed naturally (between 1%-2% annually for western hepatitis B virus [HBV] carriers and 0.5%-1% in Asian carriers).[6,7] Interferon therapy can result in HBsAg clearance, but this only occurs in a small percentage of cases when evaluated 6-12 months after therapy. In HBeAg-positive hepatitis, HBsAg loss has been reported in 3%-10% of patients without a clear relationship to the length of treatment.[8] Interferon-induced HBsAg loss tends to occur even less frequently in HBeAg-negative hepatitis, which is reflective of the generally lower rates of sustained virologic response (SVR) in this disorder. For example, Marcellin and associates recently reported the disappearance of HBsAg in 3% of a large cohort treated with 48 weeks of pegylated interferon alfa-2a, either given alone or combined with lamivudine.[9] Fortunately, the proportion of patients with SVR who undergo clearance of HBsAg increases with length of follow-up in both HBeAg-positive and HBeAg-negative hepatitis.[7,10] In the HBeAg-negative population reported by Marcellin et al. above, HBsAg clearance was observed in 11% of patients with an initial response to interferon by posttreatment year 4.[11]

From a conceptual standpoint, the degree of decline in HBsAg level during treatment might provide useful information on the probability of an SVR or eventual HBsAg clearance, and for the reasons described above, this would be particularly well suited to the treatment of HBeAg-negative hepatitis. Fortunately, ways of addressing these issues recently have become available due to the development of several commercial assay systems that can quantify HBsAg concentration (Elecsys II, Roche Diagnostics; Architect, Abbott Diagnostics; ADVIA Centaur HBsAg assay, Bayer; Hepanostika HBsAg, Biomerieux). These are now widely available in Europe and have provided an opportunity to compare the kinetics of HBsAg decline during interferon and nucleoside analogue therapy. Small clinical trials with these assays as well as a more cumbersome dilutional immunoassay have shown that serum HBsAg levels decline much more quickly during treatment with interferon as compared to nucleoside analogue treatment, a substantial decline in levels can be observed after 12 to 24 weeks of interferon, and major changes in HBsAg concentration appear to be confined to virologic responders.[12,13]

In this issue of HEPATOLOGY, two articles provide further important insights into the value of measuring HBsAg concentration in HBeAg-negative hepatitis dur-

Abbreviations: HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; SVR, sustained virologic response.

Address reprint requests to: Robert P. Perrillo, M.D., Hepatology Division, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, TX 75246. E-mail: roberper@baylorhealth.edu; fax: 214-820-8168.

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ing treatment with peginteferon.[14,15] Both studies used the Abbott Architect assay to quantify HBsAg. In the study by Moucari and colleagues, 48 patients were treated with pegylated interferon alfa-2a. The authors found that early HBsAg decline during treatment was highly predictive of SVR (defined as nondetectable HBV DNA by PCR at 1 year after treatment). Of note, the kinetics of HBV DNA decline throughout treatment were nearly identical for sustained responders and relapsers but were quite different when HBsAg decline was assessed, suggesting that measurement of HBsAg concentration may more reliably distinguish those destined to have an SVR. The authors determined that cutoff values of a 0.5 $\log_{10}$ and 1 $\log_{10}$ IU/mL decline for HBsAg concentration at treatment weeks 12 and 24, respectively, had negative predictive values of 92% and 97% for SVR. These data, therefore, indicate only a small chance of SVR should therapy be continued beyond these intervals in patients having either no change or only a minor decline in HBsAg concentration.[14] In the second study by Brunetto and associates, outcomes 3 years after treatment were assessed according to end-of-treatment decline in HBsAg concentration in 386 patients with HBeAg-negative hepatitis. These patients either had been treated with pegylated interferon alfa-2a monotherapy (n = 127), lamivudine (n = 122), or combination pegylated interferon alfa-2a and lamivudine (n = 137) for 48 weeks. The authors found that end-of-treatment HBsAg level strongly correlated with HBV DNA suppression to $\leq$ 400 copies/mL at 6 months after treatment. Moreover, an HBsAg level $<$ 10 IU/mL and on-treatment decline $>$ 1 $\log_{10}$ IU/mL at week 48 were significantly associated with HBsAg clearance 3 years after treatment. The authors also observed a 30-fold greater decline in HBsAg with peginterferon (alone or in combination) versus lamivudine, which they attributed to the immunomodulatory activity of interferon.[15]

How can the above information be helpful clinically? Both studies require prospective validation, but based on the data, one can envision several scenarios where HBsAg concentration could be an important, additive tool to HBV DNA testing. First, failure to achieve a certain decline in HBsAg concentration by 12-24 weeks of treatment might be useful as a stopping rule, thus limiting further side effects of interferon while allowing identification of patients who might benefit more from long-term nucleoside analogue viral suppression. Second, the converse would mean that reaching a predefined level of HBsAg decline might be useful to support a need for completion of 48 weeks of treatment. Third, measurement of on-treatment HBsAg concentration could help in making a decision to extend interferon therapy beyond 48 weeks in individuals with a slow but steady decline in HBsAg concentration. In short, monitoring HBsAg concentration has the potential to invoke response-directed therapy as is currently done with hepatitis C. In addition to this, a major end-of-treatment decline in HBsAg concentration might be used to predict long-term responses to treatment.

The articles by Moucari et al. and Brunetto et al. also forecast future clinical research directions. Future large-scale trials of pegylated interferon will almost certainly incorporate quantitative assessment of HBsAg. By so doing, the degree of decline in HBsAg concentration and the best interval for assessing this decline so as to most accurately predict SVR and HBsAg clearance will become better understood and validated. Although rates of HBsAg clearance have generally been nominal with nucleoside analogue therapy, a 6% rate of HBsAg loss has recently been reported in subsets of patients after 1-2 years of tenofovir.[16] Thus, quantification of HBsAg during treatment with newer, more potent nucleoside analogues could also allow indirect assessment of the potential effect these agents have on hepatic covalently closed circular DNA.

It should be mentioned that HBV genotype has been found to strongly correlate with SVR to interferon in both HBeAg-positive and HBeAg-negative hepatitis.[17,18] In a pooled data analysis of more than 1200 interferon-treated patients, SVR occurred significantly more frequently in HBeAg-positive cases with genotype A and in HBeAg-negative patients with genotype C.[18] The lowest rates of SVR with peginterferon have been shown to occur in HBeAg-negative patients infected with genotype D, and interestingly, this is the group that had the least pronounced decline in HBsAg concentration in the study by Brunetto and colleagues.[15] Thus, viral genotype might need to be accounted for when interpreting differences in the qualitative as well as quantitative aspects of response across studies.

Commercial methods to quantify HBsAg unfortunately are not currently available in the United States. This is likely to change with further study, both elsewhere in the world and under the auspice of the newly created National Institute of Diabetes and Digestive and Kidney Diseases Hepatitis B Clinical Research Network. There can be no denying that the past 5 years has been a time of great strides in the treatment of hepatitis B. However, a combination of newer methods for HBsAg quantification and innovative treatment strategies are not only likely to bring us closer to response-directed therapy, but also to achieving the more complete or "gold" response inherent to HBsAg clearance in a greater proportion of cases.

ROBERT P. PERRILLO, M.D.
Hepatology Division
Baylor University Medical Center
Dallas, TX

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