EDITORIAL

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Quantitative hepatitis B surface antigen predicts the antiviral response and hepatocellular carcinoma development in patients with chronic hepatitis B

Sung Eun Kim

Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Korea

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Chronic hepatitis B virus (HBV) infection is an important public health problem, worldwide, leading to liver-related complications such as chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) [1,2]. According to the antiviral therapy revolution against HBV, the progression to cirrhosis and the development of HCC in patients with chronic HBV infection have been effectively suppressed if low HBV DNA loads are sustained [3,4]. However, the optimal timing and strategy of antiviral therapy for chronic HBV infection are somewhat difficult. With recent advances in molecular investigations, hepatitis B e antigen (HBeAg), serum alanine aminotransferase, HBV DNA, and HBV genotype, which are associated with the response to antiviral therapy, have been identified in patients with chronic hepatitis B (CHB) [5,6]. These biomarkers predict poor clinical outcomes in patients with CHB and help to individualize their antiviral therapy. Several studies have demonstrated that a lower baseline HBV DNA level predicts HBeAg loss or HBeAg seroconversion as well as viral suppression in patients with CHB receiving antiviral therapy [5]. Baseline and on-treatment response of HBV DNA level are well-established predictors of treatment outcomes in patients with CHB on antiviral therapy.

The hepatitis B surface antigen (HBsAg) is an important biomarker of HBV infection and is qualitatively used to diagnose an HBV infection in the clinical setting. In the natural course of HBV infection, HBV DNA only originates from mature infectious particles and HBV DNA levels reflect viral replication. Because HBsAg can be derived from defective subviral particles, serum HBsAg levels reflect transcription of covalently closed circular DNA or mRNA translation and host immune control over HBV infection [6,7]. The combination of low serum HBsAg and serum HBV DNA levels can be used to predict inactive HBV carrier status and HBsAg loss after HBeAg seroconversion [8,9]. Levels of HBsAg have been reported to be a useful biomarker for evaluating viral replication and a predictor of treatment response in patients with CHB treated with interferon therapy [10]. Lee et al. [11] reported that a low HBsAg level is an important predictor of HBeAg loss in HBeAg-positive patients with CHB. These results indicate that measuring HBsAg levels may be a useful monitoring tool for CHB treatment during antiviral therapy.

In this issue, Cho et al. [12] reported

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Correspondence to
Sung Eun Kim, M.D.
Department of Internal Medicine, Hallym University Sacred Heart Hospital, 22 Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang 14068, Korea
Tel: +82-31-380-3705
Fax: +82-31-386-2269
E-mail: sekim@hallym.or.kr

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that entecavir treatment over 5 years for patients with treatment-naïve CHB and genotype C shows an excellent virologic response rate and a low resistance rate. This retrospective study included 1,009 patients with CHB whose treatment was initiated with entecavir from 2007 through 2012. Among all patients, the cumulative biochemical response rates were 81.0%, 95.0%, and 99.5% at 1, 3, and 5 years, respectively. The cumulative virologic response rates were 80.0%, 95.6%, and 99.4% at 1, 3, and 5 years, respectively. Twelve patients (1.2%) developed entecavir resistance. Interestingly, Cho et al. [12] measured HBsAg levels using stored available baseline serum samples of 271 patients (126 HBeAg-negative and 145 HBeAg-positive patients). They revealed that lower HBsAg level (< 5,000 IU/mL), lower HBV DNA level (< 6 $\log_{10}$IU/mL), and HBeAg-negative status were independently associated with the virologic response. Patients with lower HBsAg levels had a significant higher virologic response and higher HBeAg seroclearance rates, particularly patients with a high viral load. Thus, patients with the combination of HBV DNA level > 6 $\log_{10}$ IU/mL and HBsAg level > 5,000 IU/mL are at risk for a poor viral response. This study had several limitations: (1) retrospective design, and (2) a relatively small sample size to reveal the role of HBsAg level. However, this study showed long-term efficacy, the viral resistance of entecavir therapy in a real world setting, and demonstrated the factors associated with virologic response, including HBsAg level.

The association between serum HBsAg level and HCC has been elucidated in both the risk evaluation of viral load elevation and associated liver disease/cancer-hepatitis B virus (REVEAL-HBV) study and the Elucidation of Risk Factors for Disease Control or Advancement in Taiwanese Hepatitis B Carriers (ERADICATE-B) study. In the REVEAL-HBV study, serum HBsAg and HBV DNA levels were independent risk factors for HCC in HBV carriers. Serum HBsAg level was complementary to HBV DNA level in stratifying HCC risks, particularly in patients with a HBV DNA level < 200,000 IU/mL [13]. In the ERADICATE-B study, higher HBV DNA levels and serum HBsAg levels were positively correlated with the development of HCC in a dose-response manner in patients with HBV DNA levels > 2,000 IU/mL. This study also showed that serum HBsAg level ≥ 1,000 IU/mL was an independent risk factor for HCC [14].

In brief, serum HBsAg level is an important biomarker for predicting virologic response and HCC development, in addition to serum HBV DNA level in patients with CHB. Furthermore, the combination of serum HBsAg level and serum HBV DNA level could be an ideal tool for predicting the treatment response and the development HCC.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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