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LETTER TO THE EDITOR

Hepatitis B core-related antigen: Are we near a treatment endpoint?

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Abstract

Different serological and virological markers in chronic hepatitis B patients guide staging of viral infection, and initiation and response to therapy. Due to the persistence of intrahepatic covalently closed circular DNA (cccDNA) in the hepatocyte nucleus, hepatitis B is not curable. Even after undetectable hepatitis B virus DNA levels, the persistence of hepatitis B surface antigen and novel markers such as hepatitis B core-related antigen (HBcrAg) indicate the persistence of intrahepatic cccDNA. In this study, HBcrAg levels at baseline and after 24 and 48 wk of antiviral therapy predicted hepatitis B e antigen seroconversion. Due to the poor sensitivity of assays and detectable levels in HBsAg-negative patients, the long-term utility of HBcrAg needs future research.

Key Words: Hepatitis B core-related antigen; Chronic hepatitis B; Covalently closed circular DNA; Hepatitis B e antigen seroconversion; Hepatitis B virus DNA; Pregenomic RNA

Core Tip: This study highlights the predictive role of hepatitis B core-related antigen (HBcrAg) levels at baseline, and after 24 and 48 wk of antiviral therapy for hepatitis B e antigen seroconversion in chronic hepatitis B patients. The issues related to poor sensitivity of assays and detectable levels in hepatitis B surface antigen-negative patients are major concerns. Future research on the utility of HBcrAg in hepatitis B virus (HBV) flare after nucleotide cessation, occult HBV reactivation, and risk of developing hepatocellular carcinoma is also needed.

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TO THE EDITOR

We read with interest the study titled, "Serum hepatitis B core-related antigen as a surrogate marker of hepatitis B e antigen seroconversion in chronic hepatitis B" by Chi *et al*[1] in the World Journal of Gastroenterology. Hepatitis B core-related antigen (HBcrAg) and hepatitis B virus (HBV) RNA are potential serological markers of chronic hepatitis B infection and activity. In the HBV life cycle, intrahepatic covalently closed circular DNA (cccDNA) is transcribed into five RNAs of which pregenomic RNA is a precursor to synthesis of the viral genome by reverse transcription and precore mRNA is precursor to proteins hepatitis B core antigen. Hepatitis B e antigen (HBeAg) and p22cr are collectively called HBcrAg due to their identical 149 amino acid sequences. In addition, viral sequences also integrate in the host genome and can express hepatitis B surface antigen (HBsAg). Therefore, HBsAg quantification may not be exactly reflective of intrahepatic cccDNA levels. On the other hand, only cccDNA can express the viral genome. In real world settings, liver biopsy is not feasible for cccDNA quantification and a surrogate marker is needed in serum for intrahepatic cccDNA quantification. HBcrAg-related proteins can be detected in Dane particles, HBV DNA-negative Dane particles, and possibly in HBV RNA-containing virions[2]. Interestingly, nucleotide analogues (NAs) inhibit DNA polymerase and viral replication; they do not affect production of viral intermediate proteins such as HBcrAg. Therefore, even on antiviral treatment, HBcrAg can reflect cccDNA quantity and activity in hepatocytes.

This study determined the predictive role of HBcrAg for HBeAg seroconversion in chronic hepatitis B (CHB) patients. All patients were analyzed for HBcrAg, HBV RNA, and HBV DNA levels in blood and cccDNA quantification in liver biopsy specimen. Although there is treatment heterogeneity with two different cohorts of entecavir (n = 109) and pegylated-interferon (PEG-IFN) (n = 30) therapy, the authors found baseline HBcrAg levels correlating with cccDNA levels in patients with and without HBeAg seroconversion. However, the PEG-IFN group only had 30 patients, and as IFNs are immunomodulators that increase innate immune response in controlling HBV infection with higher HBeAg seroconversion rates compared to NA therapy, it may be premature to conclude that it only affects viral replication and not the production of other viral proteins. Therefore, some bias may be related to treatment heterogeneity.

This study also highlights that serum qHBcrAg levels at 24 and 48 wk of treatment better predict HBeAg seroconversion than qHBcrAg levels at baseline. Song *et al*[3] showed baseline HBcrAg levels < 4.9 log U/mL, > 2 log reduction of HBcrAg at week 28 having a positive predictive value 74% and 76%, and negative predictive value of 96% and 94%, respectively, for the prediction of spontaneous HBeAg seroconversion. In HBeAg-positive CHB patients, HBcrAg is high in the immune tolerant phase compared to the immune clearance phase. And in HBeAg-negative patients, lower HBcrAg levels are present in the inactive carrier state than in HBeAg-negative CHB. Recently Ghany *et al*[4] demonstrated a correlation of HBV RNA and HBcrAg levels with HBV DNA in different phases of CHB infection.

Wong *et al*[5] demonstrated that correlation coefficients of serum HBV DNA and HBcrAg with intrahepatic cccDNA are 0.7 and 0.64-0.7, respectively, which are similar; however, in patients on antiviral therapy with undetectable serum HBV DNA, HBcrAg is the preferred marker for estimating intrahepatic cccDNA levels. Tseng *et al*[6] recently showed risk stratification of development of cirrhosis, and its complications and liver-related mortality in CHB patients over a period of 15.9 years by baseline HBcrAg levels. Carey *et al*[7] showed that HBcrAg and HBV RNA predict clinical flares in HBeAg-negative CHB patients with suppressed HBV DNA levels on nucleotide analogue therapy. Together, HBcrAg is a promising novel serum marker but with many limitations. First, with current available assays, the lower limit of detection is 2 log U/mL, so more sensitive assays are needed. Second, one study found detectable serum HBcrAg in 40% patients with HBsAg seroclearance[8]. Finally, large-scale studies in different ethnic groups are needed to determine the predictive value of HBcrAg with certain cut-off values in clinical practice especially occult HBV reactivation, HBV flare after nucleotide analogue cessation, and risk of hepatocellular carcinoma development.

FOOTNOTES

Author contributions: Gupta T wrote and critically revised the manuscript.

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