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Hepatitis B core related antigen: Are we near to treatment end point

Gupta T et al. HBcAg: Are we near end point

Tarana Gupta
Abstract
Different serological and virological markers in Chronic hepatitis B patients guide stage of viral infection, initiation and response to therapy. Due to persistence of intrahepatic covalently closed circular DNA (cccDNA) in hepatocyte nucleus, still hepatitis B is not completely curable disease. Even after undetectable hepatitis B virus DNA levels, persistence of hepatitis B surface antigen (HBsAg) and novel markers like hepatitis B core related antigen (HBcrAg), indicate persistence of intrahepatic cccDNA. In the present study, predictive role of HBcrAg levels at baseline and sequentially after 24 and 48 wk of antiviral therapy have been documented to predict hepatitis B e antigen seroconversion. Due to poor sensitivity of assays, detectable levels in HBsAg negative patients, long term utility still 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; Pre-genomic RNA

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Core Tip: The study has highlighted predictive role of hepatitis B core related antigen levels at baseline, 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, detectable levels in hepatitis B surface antigen negative patients are major concerns. Future research for its utility in hepatitis B virus (HBV) flare after nucleotide cessation, occult HBV reactivation, risk of developing hepatocellular carcinoma should also be explored.

TO THE EDITOR
We read with interest the study “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 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 HBV life cycle, intrahepatic covalently closed circular DNA (cccDNA) transcripts into 5 RNAs of which pregenomic RNA is precursor to synthesis of viral genome by reverse transcription and precore mRNA is precursor to proteins hepatitis B core antigen, hepatitis B e antigen (HBeAg) and p22cr which due to identical 149 amino acid sequences are collectively called as HBcrAg. In addition, viral sequences also integrate in 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 viral genome. In real world settings, liver biopsy is not feasible for cccDNA quantification and we need a surrogate marker 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 like HBcrAg. Therefore, even on antiviral treatment, HBcrAg can reflect cccDNA quantity and activity in hepatocytes.

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

The present study also highlights that serum qHBcrAg levels at 24 and 48 wk of treatment better predicts 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 96% and 94% respectively for prediction of spontaneous HBeAg seroconversion. In HBeAg positive CHB patients, HBcrAg is high in immune tolerant phase as compared to immune clearance phase. And in HBeAg negative patients, lower HBcrAg levels are present in inactive carrier state than in HBeAg negative chronic hepatitis B. Recently Ghany et al[4] have demonstrated correlation of HBV RNA and HBcrAg levels with HBV DNA in different phases of CHB infection.

Wong et al[5] demonstrated that correlation coefficient of serum HBV DNA and HBcrAg with intrahepatic cccDNA is 0.7 and 0.64-0.7 respectively which is almost 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] have recently shown risk stratification of development of cirrhosis, 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. Altogether, HBcrAg is a promising novel serum marker but with many issues. Firstly, with current available assays, the lower limit of detection is 2 log U/mL. So, we need more sensitive assays. Secondly, 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 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.