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LETTER TO THE EDITOR

Hepatitis B Core-Related Antigen: A Serum Biomarker for Intrahepatic Covalently-Closed-Circular DNA

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Hepatitis B virus (HBV) infection is a major public health problem affecting more than 250 million people globally. Chronic hepatitis B (CHB) is a result of an acute, unresolved infection, that, overtime, may lead to cirrhosis and its complications such as liver failure and hepatocellular carcinoma [1]. In the last 15 years, several inhibitors of HBV polymerase, namely nucleos(t)ide analogues (NAs), have been developed and introduced in clinical practice, allowing long term suppression of HBV replication (virological response) and alanine aminotransferase (ALT) normalization (biochemical response) [2]. Hepatitis B surface antigen (HBsAg) loss and seroconversion to anti-HBs has been traditionally considered the final goal of antiviral treatment (*functional cure*). However, a *complete cure* could be achieved only with the physical elimination of HBV covalently-closed-circular DNA (cccDNA) which acts as template for all viral transcriptions and is responsible for long lasting viral persistence [3]. Currently, novel approaches aiming at HBV cccDNA elimination or inactivation are under evaluation at a preclinical level [3]. However, the possibility to measure intrahepatic HBV cccDNA is limited by liver biopsy availability and the lack of sensitive standardized PCR methods.

Hepatitis B core-related antigen (HBcrAg) is a novel serum biomarker combining the antigenic reactivity resulting from hepatitis B e antigen (HBeAg), HBV core

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antigen, and a 22 kDa core-related protein (p22cr) mainly found in HBV empty particles [4,5]. It has been reported that HBcrAg levels varied significantly among the four natural phases of HBV infection showing high predictive performance for distinguishing between HBeAg-negative inactive/quiescent carrier and HBeAg-negative hepatitis-patients (area under the curve [AUC] = 0.931) and for the discrimination between immune tolerant and immune clearance phases (AUC = 0.704) [6].

Interestingly, a significant correlation between HBcrAg and intrahepatic HBV cccDNA has been reported [7-9]. Suzuki et al., investigating the correlation between HBcrAg and intrahepatic HBV cccDNA in a cohort of Japanese CHB patients, found a positive correlation between the two parameters ($r = 0.692$, $p < 0.001$). In addition, a significant correlation between HBcrAg and intrahepatic HBV cccDNA was also observed in patients that experienced HBsAg negativization ($r = 0.482$, $p = 0.006$), suggesting a potential role of HBcrAg also in subjects with occult HBV infection [7]. More recently, Matsuzaki et al. also reported a correlation between HBcrAg and HBV cccDNA levels ($r = 0.616$, $p < 0.001$) in patients undergoing liver transplant [8]. After excluding preoperative state samples from analysis, HBcrAg remained significantly correlated to HBV cccDNA ($r = 0.402$, $p = 0.046$). Furthermore, HBcrAg and HBV cccDNA values showed similar kinetics during pre- and post-transplantation, highlighting HBcrAg reliability as a surrogate biomarker for HBV cccDNA [8]. Finally, a large-scale study including 305 liver biopsies and corresponding serum samples collected from 138 NAs-treated patients pointed out a median HBcrAg reduction at ≥ 6 years of therapy comparable to the magnitude of HBV cccDNA decay [9]. HBcrAg was strongly correlated with intrahepatic HBV cccDNA ($r = 0.70$, $p < 0.0001$). According to HBeAg status, HBcrAg was significantly correlated to HBV cccDNA levels both in the 133 HBeAg-positive patients ($r = 0.66$, $p < 0.0001$) and in the 172 -negative patients ($r = 0.45$, $p < 0.0001$). Moreover, analyzing 130 samples of HBV DNA-negative patients receiving antiviral therapy, authors observed that HBcrAg was still detectable in 101 of them, being significantly correlated with HBV cccDNA levels ($r = 0.42$, $p < 0.0001$) [8].

CONCLUSION

Since the quantification of HBV cccDNA levels will be important in clinical trials evaluating novel treatment concepts to cure HBV infection, its relationship with HBcrAg quantification renders the latter a reliable non-invasive approach useful for monitoring intrahepatic virological status.

Declaration of Interest:
All authors have nothing to disclose regarding the material discussed in the present manuscript.

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