Hepatitis B core-related antigen: a strong indicator for cessation of nucleos(t)ide analog therapy in patients with chronic hepatitis B

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With successful nucleos(t)ide analog therapy, serum hepatitis B virus (HBV) DNA titer decreases to below detection limit, alanine aminotransferase (ALT) normalizes, and fibrosis of the liver may become improved [1–4]. The incidence of hepatocellular carcinoma can be decreased as well [5–7].

However, withdrawal hepatitis frequently occurs after treatment cessation, even in patients with undetectable HBV DNA levels. As this complication is sometimes lethal [8–10], it is crucial to determine the optimal conditions for stopping nucleos(t)ide analog therapy, especially for young patients wishing to have children, the avoidance of hyper-resistant viral strains, and regulating medical expenses.

Knowledge of intrahepatic HBV replication status is the key to defining the safe conditions for nucleos(t)ide analog therapy cessation. cccDNA level is a suitable indicator for this aim, although frequent liver biopsies are needed. Serum HBV DNA was believed to be a good estimator of cccDNA. However, the correlation of HBV DNA and intrahepatic cccDNA levels is lost under the nucleos(t)ide analog treatment and cannot therefore be adopted [11]. Alternative, non-invasive markers are desired.

The possibility of discontinuation of nucleos(t)ide analogs is also affected by the clinical goal, such as no withdrawal hepatitis, no viral relapse, or long-term clinical response. The majority of patients experience viral recurrence during withdrawal, but some will not develop

hepatitis or will achieve clinical remission after a hepatitis flare.

In this issue, Jung KS et al. [12] report on virological remission (i.e., HBV DNA ≤ 2000 IU/ml) over 1 year following cessation of nucleos(t)ide therapy in patients HBeAg-positive or HBeAg-negative at the start of treatment. The virological relapse rate of each group was 57.8 and 54.4 %, respectively. Significantly and independently related factors for virological relapse were age >40 years at the start of nucleos(t)ide therapy and basal HBV DNA level $>20,000,000$ IU/ml in the HBeAg-positive group, and age >40 years at the start of nucleos(t)ide analog therapy and HB core-related antigen (HBcrAg) level >3.7 log U/ml in the HBeAg-negative group.

HBcrAg is an established viral activity marker [13]. HBcrAg levels correlated closely with those of intrahepatic cccDNA, even when HBV DNA became undetectable, during nucleos(t)ide analog therapy [11]. Thus, HBcrAg may represent a non-invasive marker of cccDNA with or without nucleos(t)ide analog therapy. We have also reported that a combination of HBsAg and HBcrAg levels at the end of nucleos(t)ide analog therapy was useful to predict long-term clinical remission [14, 15].

According to APASL guidelines, the appropriate duration of nucleoside analog administration is unknown, although HBV DNA and HBsAg are suggested as estimators of treatment efficacy [16]. There are no precise criteria for the cessation of nucleos(t)ide analog therapy in the EASL guidelines as well [17]. In the AASLD guidelines, HBsAg loss is regarded as the best predictor of sustained remission off-treatment, but is also reported to be infrequent with current therapies [18].

In this issue, the authors present clear criteria for successful discontinuation of nucleos(t)ide analog therapy using HBcrAg, which is expected to contribute to the

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enhancement of chronic hepatitis B patient management. Their study also underscores the importance of measuring multiple HBV antigens in addition to HBV DNA to better estimate the behavior of HBV in the liver.

Compliance with ethical standards

Conflict of interest The author declares there is no conflict of interest.

References

1. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2006;354:1001–10.
2. Lai CL, Shouval D, Lok AS, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med*. 2006;354:1011–20.
3. Lai CL, Chien RN, Leung NW, et al. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *N Engl J Med*. 1998;339:61–8.
4. Suzuki Y, Kumada H, Ikeda K, et al. Histological changes in liver biopsies after one year of lamivudine treatment in patients with chronic hepatitis B infection. *J Hepatol*. 1999;30:743–8.
5. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med*. 2004;351:1521–31.
6. Matsumoto A, Tanaka E, Rokuhara A, et al. Efficacy of lamivudine for preventing hepatocellular carcinoma in chronic hepatitis B: a multicenter retrospective study of 2795 patients. *Hepatol Res*. 2005;32:173–84.
7. Hosaka T, Suzuki F, Kobayashi M, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology*. 2013;58:98–107.
8. Honkoop P, de Man RA, Niesters HG, et al. Acute exacerbation of chronic hepatitis B virus infection after withdrawal of lamivudine therapy. *Hepatology*. 2000;32:635–9.
9. Honkoop P, de Man RA, Heijtkink RA, Schalm SW. Hepatitis B reactivation after lamivudine. *Lancet*. 1995;346:1156–7.
10. Liu F, Wang L, Li XY, et al. Poor durability of lamivudine effectiveness despite stringent cessation criteria: a prospective clinical study in hepatitis B e antigen-negative chronic hepatitis B patients. *J Gastroenterol Hepatol*. 2011;26:456–60.
11. Suzuki F, Miyakoshi H, Kobayashi M, Kumada H. Correlation between serum hepatitis B virus core-related antigen and intra-hepatic covalently closed circular DNA in chronic hepatitis B patients. *J Med Virol*. 2009;81:27–33.
12. Jung KS, Park JY, Chon YE, et al. Clinical outcomes and predictors for relapse after cessation of oral antiviral treatment in chronic hepatitis B patients. *J Gastroenterol*. 2016;51:830–9.
13. Kimura T, Rokuhara A, Sakamoto Y, et al. Sensitive enzyme immunoassay for hepatitis B virus core-related antigens and their correlation to virus load. *J Clin Microbiol*. 2002;40:439–45.
14. Matsumoto A, Tanaka E, Suzuki Y, et al. Combination of hepatitis B viral antigens and DNA for prediction of relapse after discontinuation of nucleos(t)ide analogs in patients with chronic hepatitis B. *Hepatol Res*. 2012;42:139–49.
15. Tanaka E, Matsumoto A. Guidelines for avoiding risks resulting from discontinuation of nucleoside/nucleotide analogs in patients with chronic hepatitis B. *Hepatol Res*. 2014;44:1–8.
16. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int*. 2016;10:1–98.
17. European Association For The Study Of The Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol*. 2012;57:167–85.
18. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016;63:261–83.