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EDITORIAL

Stopping oral antiviral treatment to cure chronic hepatitis B, is it in sight?

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The treatment of chronic hepatitis B (CHB) patients has evolved dramatically over the past two decades. Currently, oral nucleos(t)ide analogues (NA) with potent viral suppression and a high genetic barrier to resistance, i.e., entecavir, tenofovir disoproxil and tenofovir alafenamide, are recommended as first-line antivirals. Long-term NA treatment can suppress hepatitis B virus (HBV) replication, reverse liver fibrosis, and reduce the risk of hepatocellular carcinoma (HCC) [1].

In the era of oral antiviral treatment, functional cure and finite treatment are the few unmet needs left for clinicians to address. In 2012, Hadziyannis et al. linked stopping treatment to the functional cure of CHB [2]. Surprisingly, they found that treatment discontinuation could lead to as high as 40% HBsAg loss during up to 6-year post-treatment follow-up among 33 HBeAg-negative, genotype D-infected, NA-naive CHB patients who stopped adefovir monotherapy after 4–5 years of successful treatment. Non-re-treatment and higher ALT levels at the end of treatment (EOT) were associated with a higher incidence of HBsAg loss [2]. Thereafter, a growing number of studies showed that HBsAg could be cleared after stopping NA treatment due to the activation of the host immune response along with off-treatment relapse in Asian and Caucasian HBeAg-negative patients [3, 4]. In a randomized controlled trial (RCT) in Europe (FINITE study), 42 HBeAg-negative, mainly Caucasian patients stopped or continued NA therapy; 19% of the patients in the treatment cessation group achieved HBsAg loss by off-treatment week 144, whereas none of the patients in the continuation group cleared HBsAg [3]. A larger retrospective study from Taiwan also reported high HBsAg loss among 691 patients, with an annual incidence of 1.8% [4]. However, there is also strong opposition that claims that the few patients achieved HBsAg loss after treatment cessation [5, 6]. The HBsAg decline was similar between the treatment cessation and continuation groups (0.2 vs. 0.1 $\log_{10}$ IU/mL at off-treatment week 72) among 67 HBeAg negative, mainly Asian CHB patients in an RCT [5]. The opposite results among the above results may be explained by different ethnicities (Asian vs. Caucasian), pre-treatment HBeAg status (positive vs. negative), HBV genotypes (B and C vs. A and D) and retreatment criteria. Therefore, it is still unclear whether stopping NAs can improve the functional cure.

In this issue of *Hepatology International*, Chen et al. compared the kinetics of qHBsAg between HBeAg-negative non-cirrhotic CHB patients who discontinued ($N=250$) and maintained ($N=231$) entecavir therapy in Taiwan [7]. The Taiwan government offered oral therapy reimbursement for only 3 years for non-cirrhotic CHB patients [8]. Thus, CHB patients in Taiwan may discontinue or remain (self-pay) on treatment after the government terminates the coverage of costs for treatment. The reimbursement policy provides the opportunity for Taiwan hepatologists to investigate the outcome after stopping oral therapy. Chen et al. found that patients in the discontinued group without retreatment experienced a significantly larger qHBsAg drop and higher HBsAg loss rate than patients in the maintained group. More importantly, they described the qHBsAg kinetics among patients with different relapse and treatment patterns in the discontinued group and found the following: (1) discontinued patients without retreatment exhibited a significantly larger qHBsAg drop after stopping treatment than before stopping. (2) Patients with persistent virological suppression and those who experienced clinical relapse without retreatment had a greater post-treatment qHBsAg decline than those who experienced virological relapse but no clinical relapse or retreatment and those who experienced HBV relapse and underwent retreatment. (3) Patients who experienced HBV relapse and underwent retreatment had a similar qHBsAg drop to those in the maintained group.

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This important study provided valuable detailed data on what happens to qHBsAg after stopping oral therapy by stratifying patients according to relapse/non-relapse and re-/non-re-treatment, which can trigger more speculation about the benefit of treatment discontinuation.

Despite increasing evidence of an increased HBsAg loss rate after treatment cessation, the effectiveness of treatment cessation remains a subject of debate, largely related to concerns regarding the harms of treatment cessation. Chen et al. [7] reported two types of HBsAg clearance after treatment cessation: one is a smooth transition from full viral suppression during therapy to full viral clearance off therapy without any viral rebound, while the other is an initial viral and clinical flare followed by immune control. The second is much more frequent than the first and is not what physicians and patients want to encounter.

Clinical flares are a double-edged sword that could help clear HBsAg to realize a functional cure; however, necrosis, inflammation and hepatic regeneration, which are all associated with a clinical flare, are well-known risk factors for HBV-related HCC. Theoretically, patients cured by clinical flares still face a risk of HCC development. Chen et al. reported that there was no significant difference in HCC incidence between the discontinued and maintained groups. However, the patients with retreatment and maintained treatment had a trend of lower risk of HCC than those without retreatment (2.9% [10/349] vs. 4.5% [6/132]). Therefore, before encouraging physicians and patients to stop oral therapy, it is warranted to study the long-term outcomes of patients cured by clinical flares compared to long-term treated patients with persistent viral suppression.

It is also important to understand whether the patient would have a good chance of sustained response and low risk of fatal outcome after treatment cessation. In general, 70% of HBeAg-negative patients may experience viral relapse after stopping treatment [9]. The persistence of covalently closed circular DNA (cccDNA) in the hepatocyte nuclei even after long-term NA therapy is the key reason for viral rebound after stopping treatment. Unfortunately, no reliable and satisfactory predictor of post-NA remission has been identified to date. The levels of HBsAg, HBcrAg and HBV RNA are associated with cccDNA activity and have been proposed to be used to guide safe discontinuation. The Japan Society of Hepatology (JSH) suggested combining HBsAg < 80 IU/mL and HBcrAg < 3 $\log_{10}$ U/mL to guide NA cessation in patients with long-standing viral suppression [10]. Hsu et al. further modified the JSH score by incorporating 3 other variables (ALT, age and tenofovir use), which showed better predictive value for clinical relapse [11]. More recently, Fan et al. proposed that patients who were double negative for both HBV DNA and RNA had a significantly lower risk of off-treatment relapse than those with either positive HBV DNA or RNA [12]. Besides, combining HBV RNA and HBcrAg also performed satisfactorily in predicting clinical relapse and HBsAg loss after treatment cessation in HBeAg-positive CHB patients. No clinical relapse occurred among patients with negative HBV RNA and HBcrAg < 4 $\log_{10}$ U/mL at EOT [13]. Therefore, it is recommended that the above two combinations may be used to guide NA discontinuation in clinical practice. All the above recommendations are yet to be supported by randomized trials. Moreover, it is still necessary to explore more reliable biomarkers or their combinations to guide discontinuation.

Last, the potential for physical, financial and psychological harms caused by treatment cessation should also be considered. Physical harm can result from close monitoring testing and extend beyond medical complications to include discomfort. Financial harms can include anticipated or actual costs of laboratory tests, hospitalization expenses if severe clinical flares occur, as well as some indirect costs such as missed work. Psychological harms include anticipation or fear of abnormal results and reactions of depression, anxiety or worry of HCC risk after stopping therapy. To date, few studies have quantified the above harms.

In conclusion, the current available studies of treatment cessation are not sufficient or comprehensive enough to lead to a widespread paradigm shift in recommending stopping oral therapy in HBeAg-negative CHB patients with sustained viral suppression. Before the advent of novel anti-HBV drugs with new targets and new mechanisms, our key aim is to reduce the liver-related mortality that is mainly caused by HCC, which is also the goal of the World Health Organization [14].

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Compliance with ethical standards

Conflict of interest JLH has received consulting fee from AbbVie, Arbutus, Bristol Myers Squibb, Gilead Sciences, Johnson &Johnson, Roche and received grants from Bristol Myers Squibb and Johnson & Johnson. RF declares no conflicts of interest.

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