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Short Communication

Nucleos(t)ide Analogue Treatment in Chronic Hepatitis B: Continuous Versus Discontinued Strategy

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There are approximately 240 million people with chronic hepatitis B virus (HBV) infection worldwide [1]. The goal of treatment for chronic hepatitis B (CHB) is to improve the life quality and survival of infected people by prevention of disease progression to cirrhosis, hepatocellular carcinoma (HCC) and death. The optimal endpoint of CHB therapy is hepatitis B surface (HBsAg) seroclearance, so-called "functional cure". Current guidelines recommend pegylated interferon and oral nucleos(t)ide analogues (NUC) including entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) as the first line choices of treatment [2-4]. Long-term NUC therapy can lead to persistent viral suppression, but the rate of HBsAg seroclearance is low [5]. As the studies have emerged recently that patients with discontinued NUC therapy would have a higher rate of HBsAg seroclearance [6-8], current guidelines have suggested that NUC discontinuation can be considered in selected CHB patients [2-4] and therefore, the indefinite NUC therapy in CHB patients needs to be re-discussed.

Continuous NUC treatment

Long-term treatment with potent NUCs such as ETV and TDF will lead to persistent viral suppression in almost all CHB patients [9-11]. After a median duration of 6-year ETV treatment, regression of liver fibrosis (≥1-point decrease in Ishak score) was observed in 88% and reversal of cirrhosis was identified in 4 of 10 patients with cirrhosis at baseline [12]. TDF was associated with overall regression of fibrosis in 51% and reversal of cirrhosis in 74% of patients through 5-year treatment [10]. In a landmark trial with placebo-controlled, double-blind, parallel group study of patients with chronic HBV infection, the patients with advanced liver fibrosis or cirrhosis were randomized to receive lamivudine or placebo [13]. Those in lamivudine treatment arm had a significantly reduced risk of disease progression (hepatic decompensation, HCC, spontaneous bacterial peritonitis, gastro-esophageal bleeding or death related to liver disease), as compared to placebo arm (adjust hazard ratio [HR] 0.45, p = 0.001). Subsequent studies also showed significantly lower HCC incidence in cirrhotic patients after long-term antiviral therapy than historical untreated controls (HR, 0.55, p = 0.049 in Hong Kong; HR, 0.37, p = 0.030 in Japan and HR, 0.40 in Taiwan) [14-16], as well as hepatic complications and liver-related mortality [14,16].

The benefits of long-term NUC therapy in CHB patients include successful DNA suppression, ALT normalization, promote fibrosis regression and prevention of hepatic untoward events and HCC. However, the long-term safety is still a concern. ETV or TAF is preferred in patients of age > 60 years, with bone diseases (such as osteoporosis, history of fragility fracture) and renal abnormalities (estimated glomerular filtration rate < 60 mL/min/1.73m^2, proteinuria, low phosphate and hemodialysis) [2,4]. TAF is suggested in patients with lamivudine resistance and coinfection with human immunodeficiency virus.

Discontinued NUC treatment

Virological relapse

The rate of virological relapse after discontinuation of NUC therapy is high. In a systemic review including 25 studies investigating clinical outcomes of 1716 patients with cessation of NUC therapy showed virological relapse rates of 50% and 70% in HBeAg-positive

and HBeAg-negative patients, respectively [17]. Age, male gender, high baseline HBV DNA, pre-existing lamivudine resistance, low baseline alanine aminotransferase (ALT), higher HBsAg level at end of treatment (EOT) and shorter duration of treatment and consolidation therapy are associated predictors of virological relapse [18]. A study including 95 HBeAg-negative patients with discontinuation of ETV treatment for a mean of 2 years found that the one-year virological relapse rate decreased from 45.3% to 29% in those with baseline HBV DNA < 200,000 IU/mL [19]. Another study by Chen., *et al.* recruiting 83 HBeAg-negative and 169 HBeAg-positive patients showed that age of 40 years and baseline HBsAg level at 1000 IU/mL was associated with HBV relapse in HBeAg-positive patients and age of 55 years and EOT HBsAg level at 150 IU/mL was associated with HBV relapse in HBeAg-negative patients [20]. Furthermore, earlier clinical relapse was observed in patients with discontinuation of TDF than those with ETV cessation [21,22].

HBsAg seroclearance

HBsAg seroclearance occurred in 39% of the untreated patients in a study of 33 HBeAg-negative Caucasian patients who stopped adefovir dipivoxil after treatment for 4 or 5 years [6]. The first randomized study including 44 HBeAg-negative non-cirrhotic patients with TDF treatment for ≥ 4 years showed 4 lost HBsAg in 21 patients stopping TDF, but none in those with continuous therapy [7]. A most recent large-scale study in Taiwan recruiting 691 HBeAg-negative CHB patients with discontinuation of NUC therapy showed a 6-year cumulative incidence of 36% in HBsAg seroclearance and an annual incidence of 6.3%, which was much higher than the 0.33% annual HBsAg seroclearance rate in patients with long-term NUC therapy [23]. The predictors of HBsAg seroclearance included time to undetectable HBV DNA (< 12 weeks), HBsAg reduction (≥ 1 log IU/mL), EOT HBsAg (< 100 IU/mL) and no clinical relapse or clinical relapse without retreatment. Higher incidence of HBsAg seroclearance was also found in HBeAg-negative cirrhotic patients who discontinued NUC therapy than those with continuous therapy ($p < 0.001$) [24] and the incidence of HCC development was comparable between patients with continuous and discontinued NUC therapy ($p > 0.05$) [24,25].

There were cirrhotic patients with development of hepatic decompensation and even death after stopping NUC therapy, but the rate was low [8]. Therefore, off-therapy follow-up with close monitor cannot be overemphasized. The patients with NUC discontinuation are suggested to check ALT monthly in the first 3 months and every 3 - 6 months afterwards for 1 - 2 years and every 6 months thereafter. HBV DNA assay is recommended every 3 months for 1 - 2 years [18]. Timely retreatment is indicated in patients with non-beneficial clinical relapse and ineffective immune clearance. Large-scale studies and consensus in the timing of retreatment are needed in the future.

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Volume 5 Issue 8 August 2018