Convenient chronic hepatitis B candidates for antiviral cessation and retreatment after relapse: When and who?

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Chronic hepatitis B (HBV) infection has been treated with nucleos(t)ide analogs (NAs) successfully in recent years, especially with entecavir (ETV) and tenofovir disoproxil fumarate (TDF) with their ability to inhibit the HBV replication, normalize the laboratory, and improve the histology in nearly all patients (1,2). Unfortunately, NAs can't eradicate HBV from the liver, and they rarely eliminate the hepatitis B surface antigen (HBsAg), which is an ideal but a remote and unrealistic target for the discontinuation of NAs therapy.

In addition, concerns with regard to an indefinite NAs therapy, such as cost, adherence, and safety issues with the long-term use has led to a search for the optimum candidates for the antiviral cessation. In 2008, the Asian Pacific Association for the Study of the Liver (APASL) recommended to consider discontinuing NAs in hepatitis B e-antigen (HBeAg)-negative chronic HBV patients if HBV DNA has been undetectable on three separate occasions, each at least 6 months apart. On the other hand, European and American guidelines recommend to continue NAs in patients with HBeAg-negative chronic HBV, unless they achieve the HBsAg loss, which means the majority of such patients should take indefinite therapy (3,4). Two recent studies have been published in the latest issue of Hepatology to shed light on this dilemma.

Jeng et al. (5) aimed to investigate the factors affecting increased probabilities of HBsAg seroclearence after the cessation of NAs. They examined a total of 1,075 HBeAg-negative patients who were successfully treated with NAs for a median time of 156 (61-430) weeks and found out that only five of them showed HBsAg seroclearence during treatment. Of the 1,075 patients, 691 who remained HBsAg-seropositive had stopped NA therapy according to the APASL criteria and were recruited for the prospective follow-up for a median period of 155 (2-614) weeks. During off-therapy follow-up, the HBsAg seroclearence was seen in 42 patients, which was greater than patients on therapy. The 6-year cumulative and estimated annual incidence rate of HBsAg seroclearence in the off-therapy patients was 13% and 1.78% respectively, which were both greater than in the on-therapy patients. The HBsAg seroclearence rates after antiviral cessation did not differ among patients with and without cirrhosis (n=19 vs n=23, p=0.531). During the follow-up period after the cessation of NA therapy, clinical and virologic relapse was observed in 419 (60.6%) and 547 (79.2%) patients, respectively. A total of 269 patients were retreated because of the clinical relapse, and 12 received retreatment because of virologic relapse. As a result of the multivariate analysis, patients with shorter time to undetectable HBV DNA (<12 weeks), greater HBsAg reduction during therapy (>1 log10), lower end of treatment HBsAg level (<100 IU/ml), and sustained response (without clinical and/or virologic relapse) were found to be associated independently with HBsAg seroclearence during the off-therapy follow-up. Of these parameters, sustained response had the highest significance level with an adjusted hazard ratio, which may reflect that such patients might have already achieved a better immune control before treatment discontinuation and explain why the incidence of HBsAg seroclearance was higher in the off-therapy group.

The other study comprises a prospective three-center study with 130 HBeAg-negative non-cirrhotic chronic HBV patients, whose therapies were discontinued after a successful therapy with NAs for at least 24 months and followed up for a median period of 15 months after cessation (6). The main objective of this study was to evaluate whether the definition of relapse had an impact on remission rates and probability of retreatment after the NA discontinuation. To illuminate this uncertainty, var-

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ious definitions of virologic and combined virologic and biochemical relapse were assessed (HBV DNA>200, >2000, >20,000, >100,000 IU/ml, and ALT>upper limit of normal (ULN), >2x ULN, >3x ULN, >5x ULN, >10x ULN). As expected, cumulative rates of virologic relapse decreased at 6-12-24 months with each log addition to HBV DNA cut-off levels used for relapse definition (73%-82%-90%, 56%-71%-83%, and 32%-48%-63% for 200; 2,000; and 20,000 IU/mL, respectively). Up to 55% of patients developed combined HBV DNA>2000 IU/mL and ALT>ULN, while the cumulative rates for combined ALT elevations >2x ULN and HBV DNA>2000 IU/mL were approximately 40%. The cumulative probability of retreatment rates for 6-12-24 months after NA discontinuation was 15%-22%-40%, respectively. If relapse is defined as HBV DNA>2000 IU/mL and ALT>ULN; use of TDF instead of ETV at treatment discontinuation, longer duration of on-therapy remission were the only factors associated with the probability of relapse according to the multivariable analysis. Despite the high rates of relapse by the various definitions, only 22%-40% were retreated after 12-24 months of post-NA follow-up due to the strict predetermined criteria for retreatment, which were ALT>10×ULN or ALT>5×ULN and total bilirubin>2 mg/dL or ALT>3×ULN and HBV DNA>100,000 IU/mL in two centers and ALT>2×ULN twice 3 months apart and HBV DNA>2000 IU/mL, total bilirubin >2 mg/dL or prolongation of prothrombin time of ≥3 seconds in the other center. The majority of patients would have been retreated if indications for retreatment were considered to be HBV DNA>2000 IU/mL combined with ALT>ULN, whereas majority of patients were not retreated when more stringent criteria for retreatment initiation were adopted. The limitation of the study was that one center used different criteria for retreatment from the other two centers. However, the retreatment rates were not different between centers, therefore this difference does not seem to have a big impact on results.

These two studies contribute to the literature with the following conclusion: the HBsAg seroclearence is more frequently seen in the follow-up period after the cessation of NA, especially in those with sustained virological and clinical remission, which may be theoretically explained by achieving a better immune control before treatment discontinuation. These detected higher rates can be attributed to patients with shorter time to undetectable HBV DNA (<12 weeks), greater HBsAg reduction during therapy (>1 log10), lower end of the HBsAg treatment level (<100 IU/mL), and sustained response (without clinical and/or virologic relapse). More stringent predetermined criteria for retreatment result in lower rates of retreatment, which may avoid potential unnecessary life-long treatment. Further studies are warranted to determine the criteria for the optimal timing of retreatment and other factors affecting the HBsAg seroclearence. Surrogate markers of intrahepatic viral replication, such as the hepatitis B core-related antigen and HBV RNA, can be promising for this field in the future (4,7). Until then, the decision of antiviral cessation will remain dubious in patients without HBsAg seroclearence.

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