Cessation of nucleos(t)ide analogues for patients with chronic hepatitis B in Taiwan: Risky but inevitable

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Long-term nucleos(t)ide analogue (NA) therapy for patients with chronic hepatitis B (CHB) is safe and well tolerated; achieves potent viral suppression, regression of liver fibrosis and cirrhosis; and reduces the incidence of liver-related adverse outcomes, such as complications of cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC).[1] The ideal treatment endpoint for CHB is the clearance of hepatitis B surface antigen (HBsAg), which is considered a functional cure of HBV infection. However, HBsAg seroclearance is uncommon by current treatment strategies,[2,3] and therefore most CHB patients require NA therapy indefinitely, which raises the concerns of patient adherence and unknown safety over years. In addition, indefinite NA therapy may result in a considerable financial burden on healthcare systems. In many countries, patients are not fully reimbursed for the costs of NA therapy. For example, NA therapy for patients with HBeAg-negative CHB was reimbursed for only 36 months regardless of the treatment response by the National Health Insurance in Taiwan.

For these reasons, the Asian Pacific Association for the Study of the Liver (APASL) set up a stopping rule that cessation of NA therapy can be considered in HBeAg-positive CHB patients with HBeAg seroconversion and undetectable HBV DNA for at least 12 months, and in HBeAg-negative CHB patients treated for at least 2 years with undetectable HBV DNA documented on three separate occasions 6 months apart.[4,5] High rate of virological relapse and clinical relapse has been reported after cessation of NA even in patients achieving the APASL stopping rules.[6,7] Nevertheless, the risk of disease progression after stopping NA therapy remains unclear.

In the February issue of the Journal, Su et al[8] reported the incidence of liver decompensation, hepatic failure, and mortality after discontinuation of NA therapy.

In this study, among the 51 574 CHB patients who received NAs in the Taiwan National Health Insurance Research Database, 8631 patients who continued NA therapy and 8631 propensity-score matched patients who stopped NA therapy after initial 1.5 years treatment were analyzed. The author reported significantly lower risks of liver decompensation (1.05% vs 2.13%), hepatic failure (0.35% vs 0.63%), and overall mortality (1.67% vs 2.44%) in patients continuing NA therapy than those stopping NA during the 18-month follow-up period. After adjusting for potential confounders, NA continuous therapy was associated with reduced risks of liver decompensation (hazard ratio [HR]: 0.47), hepatic failure (HR: 0.53), and overall mortality (HR: 0.67). The author concluded that NA continuous therapy is associated with reduced risks of liver decompensation, hepatic failure, and overall mortality.

Although this study reported the better outcomes in patients who continued NA therapy, it has several limitations. First, the Taiwan National Health Insurance Research Database could not provide clinical data especially the virological response, including HBV DNA suppression or HBeAg seroconversion. Therefore, whether patients discontinued NA under adequate treatment response could not be evaluated. Second, the NAs in this study included lamivudine, adefovir, telbivudine, entecavir, and tenofovir, while the off-therapy cohort enrolled patients before 2008. Since entecavir was available after 2005, and tenofovir was available since 2008, the off-therapy cohort could only receive low potency NAs lamivudine, adefovir, telbivudine, with higher risk of drug resistance and HBV reactivation, which could lead to the poorer outcomes in this group. Third, the median NA therapy duration was only 1.28 and 2.12 years in the off-therapy cohort and the treatment cohort, respectively. Therefore, most patients in this study did not receive long enough NA therapy, and by definition, did not achieve the APASL stopping rules. Fourth, the observation period started from 1.5 years after the first NAs prescription to 3 years after the first NAs prescription. That means significant proportion of patients in the treatment cohort also stopped NA therapy in the last year of observation. Furthermore, the risk of disease progression for patients who stop NA after 3 years of treatment remains unanswered.

Stopping NAs remains a controversial issue. Some studies showed the potential benefit of stopping NA therapy, with relatively high HBsAg loss rates, but also observed a variable rate of virological relapse that sometimes led to dangerous

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flares.[9,10] In the Toronto STOP study, the largest prospective randomized controlled trial to date on NA withdrawal in CHB, 27% of patients had sustained response, 71% relapsed, and 2% achieved HBsAg loss 72 weeks after stopping NA therapy.[11] Pretreatment HBeAg-positive patients were three times more likely than HBeAg-negative patients to require retreatment for relapse after stopping NA, and HBsAg levels in the stop group declined only marginally and were not different from the NA continuation group. The findings in the Toronto STOP study suggest that stopping NA therapy confers little benefit. Although some studies suggested that an HBsAg level <100 IU/mL at the end of treatment could be a useful marker for deciding when to safely discontinue NAs therapy, currently there is still lack of a reliable predictor of relapse.

Indefinite NA therapy until HBsAg seroclearance is the safest way for patients with CHB, but it is not feasible under current policies of the National Health Insurance in Taiwan. In Taiwan, NA therapy is reimbursed for HBeAg-positive patients until 12 months after HBeAg loss, which fulfilled the current APASL stopping rule for HBeAg-positive case. However, in HBeAg-negative patients, NA therapy was reimbursed for 3 years regardless of treatment response. Therefore, some patients prematurely discontinued NA therapy and faced the high risk of virological and viral relapse. For patients who stopped NA without a significant clinical relapse, low-grade viremia remains common but no further retreatment will be applied due to the reimbursement policy. The risk of liver disease progression and HCC in this population remains unclear. A previous study showed that CHB patients with low-level viremia still carried a higher risk of the development of HCC than those with undetectable HBV DNA.[12]

Despite these concerns, NA treatment cessation is inevitable in most CHB patients in Taiwan under current National Health Insurance Policy. A close monitoring schedule must be reinforced after stopping NA, and retreatment should begin early if evidence of relapse. Long-term outcomes after stopping NA must be further evaluated, and monitoring of liver fibrosis and HCC surveillance remains needed.

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