

## Reduction or cessation of antiviral agents in hepatitis B virus carriers treated with biologic agents

Sirs,

Antiviral agents are generally prescribed in hepatitis B virus (HBV) carriers in addition to biologic agents (1). However, the antiviral prophylaxis cannot be sustained in some patients because of economic cost or adverse events. In this study, the outcome of reducing or discontinuing antiviral agents in HBV carriers during treatment with biologic agents was assessed.

The medical records of 27 HBV carriers treated with biologic agents in a tertiary hospital between January 2005 and December 2016 were reviewed with the approval of the Asan Medical Center Institutional Review Board (IRB number: 2016-1034). Laboratory data were collected to evaluate liver function and serum HBV DNA along with assessment of HBV hepatitis flare.

The HBV carriers had been diagnosed with rheumatoid arthritis (n=8), Crohn's disease (n=11), ankylosing spondylitis (n=6), ulcerative colitis (n=1), and psoriatic arthritis (n=1). The biologic agents were given for a median of 39 months (interquartile range (IQR), 26–66). Three of the 12 HBV carriers not receiving HBV prophylaxis experienced hepatitis flare at 3, 3, and 66 months, respectively, after initiation of biologic agents. On the other hand, there were no flares for 39 months (IQR, 27 to 62) among the 15 patients receiving HBV prophylaxis.

Among the HBV carriers receiving biologics and HBV prophylaxis concomitantly, one CD patient treated with infliximab received standard tenofovir prophylaxis for 9 months. HBV DNA titres of the patient was reduced from 530 IU/mL (at starting administration of biologics) to undetected level (<15 IU/mL, after 9 months). After that, the patient had the dose of the HBV regimen (tenofovir) reduced to alternate days because of an adverse drug reaction (diarrhoea), and since the dose-reduction, there has been no hepatitis flare, and no HBV DNA has been detected for 21 months. In another 2 HBV carriers (an AS patient treated with etanercept and a RA patient

with etanercept, adalimumab, and rituximab), standard HBV prophylaxis (lamivudine) was stopped after 37 and 5 months, respectively. No hepatitis flares occurred in these patients for over 87 and 119 months, respectively, of follow-up and their HBV DNA titres have remained low (Table I). In contrast, in the group without any HBV prophylaxis, 2 of 3 HBV carriers experienced hepatitis flares within 3 months of starting treatment of biologics.

Several studies reported that low-dose entecavir (a tenth or a fifth part of the standard dose) and tenofovir (a quarter of the standard dose) suppressed viral replication (2–4). It is therefore possible that no flares occurred after reduction of HBV prophylaxis in the patients in the present study for these reasons. Considering that a high titre of HBV DNA is an important risk factor for HBV reactivation in immunocompromised patients (5), reduction of the HBV regimen may be safe after negative conversion of HBV DNA by standard prophylaxis.

Previous studies suggested that the risk of infection is high at the beginning of TNF- $\alpha$  inhibitor treatment (6, 7), while the risk of infection is lower than that of conventional disease-modifying anti-rheumatic drugs by the third year of dosing (7, 8). Based on such findings, it seems that the administration of lamivudine for 37 and 5 months, respectively, was responsible for the absence of hepatitis flare during the critical period in our cases.

In conclusion, it is important to administer HBV regimens continuously and monitor them regularly in HBV carriers treated with biologic agents. However, there was no hepatitis flares when HBV prophylaxis was stopped or reduced to half in the present study. If the titre of HBV DNA decreases or negative conversion occurs during standard HBV prophylaxis in HBV carriers who have to be treated with biologics, reducing or stopping HBV prophylaxis might be considered in certain circumstances.

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**Table I.** The three HBV carriers whose HBV regimens were stopped or reduced.

	Patient 1 (M/40)	Patient 2 (F/39)	Patient 3 (F/49)
Dose-reduction or stopping	Stopping	Stopping	Dose-reduction
Underlying disease	Ankylosing spondylitis	Rheumatoid arthritis	Crohn's disease
Biologic agent	Etanercept	Etanercept Adalimumab Rituximab	Infliximab
Dose of glucocorticoid* (mg/day)	0	5	0
Concomitant immunosuppressant (dose)	None	None	Azathioprine (25 mg/day)
Antiviral agent / treatment duration at the standard dose	Lamivudine (37 months)	Lamivudine (5 months)	Tenofovir (9 months)
Follow up duration after stopping or dose-reduction	87 months	119 months	21 months
AST / ALT (IU/L) at starting biologic agent	40 / 29	35 / 40	17 / 12
HBeAg at starting antiviral agent	Negative	Negative	Negative
HBV DNA (IU/mL) at stopping or dose-reduction	$2.4 \times 10^3$	$7.2 \times 10^7$	Negative
Follow up HBV DNA (IU/mL) after stopping or dose-reduction (months)	$4.9 \times 10^2$ (87 months)	$4.2 \times 10^4$ (75 months)	Negative (21 months)

\* Prednisolone equivalent. AST: aspartate aminotransferase; ALT: alanine aminotransferase; HBV: hepatitis B virus.