

Change in hepatitis B virus DNA status in patients receiving chronic immunosuppressive therapy for moderate-to-severe skin disease

Dear Editor,

Hepatitis B virus (HBV) infection poses a global health burden. Clinically, patients may present with chronic HBV infection, occult HBV infection, and fulminant hepatic failure. In 2010, the hepatitis B surface antigen (HBsAg) seroprevalence in Singapore was 3.6%.¹

Patients with dermatological conditions receive prolonged corticosteroid and other immunosuppressive therapy for moderate-severe skin diseases. All patients with chronic HBV infection are at risk of HBV reactivation. The 2015 American Gastroenterological Association Institute Guidelines indicate that patients subjected to prolonged courses (greater than 4 weeks) of moderate to high dose (at least 10mg prednisolone daily equivalent being moderate dose, and greater than 20mg prednisolone daily equivalent being high dose) may lead to HBV reactivation in 1–10% of patients.² There are no Singapore data on the outcome of chronic hepatitis B patients receiving oral or topical steroid and/or other immunosuppressive therapy for skin conditions.

We conducted a retrospective study from 2016 to 2020 of 25 patients from the dermatology outpatient clinic at the National University Hospital, a Singapore tertiary hospital. This study was approved by the NHG Domain Specific Review Board.

The inclusion criteria were: patients above 21 years old, possessing dermatological conditions that required them to be on chronic systemic immunosuppression for more than 3 months, having had either resolved or chronic HBV infection. Treatment with topical clobetasol ointment for bullous pemphigoid, which has been shown to be equivalent to systemic steroids, was also included.³ The exclusion criteria included: previous or concomitant biologic therapy at the point of recruitment, pre-existing chronic liver disease with evidence of cirrhosis, haematological malignancy, immunodeficiency syndromes, pregnancy or breastfeeding, ongoing active systemic infection, previous stem cell or solid organ transplant, and known hepatocellular carcinoma.

Resolved infection was defined as the presence of positive anti-hepatitis B core antibody (anti-HBc total Ab) with negative HBsAg, while chronic HBV infection was defined as a state where HBsAg was positive, with positive anti-HBc total antibody.

For patients with chronic HBV infection, reactivation was defined to have occurred when any one of the

following is fulfilled: (1) ≥ 2 log (100-fold) increase in HBV DNA compared to the baseline; (2) HBV DNA ≥ 3 log (1,000) IU/mL in those with baseline undetected HBV DNA; or (3) HBV DNA ≥ 4 log (10,000) IU/mL, if the baseline level unavailable. For patients with resolved HBV infection, the criteria used are detection of HBV DNA or development of HBsAg (reverse seroconversion).

Hepatitis flare was defined as an event with abrupt rise of alanine aminotransferase (ALT) levels to >5 times the upper limit of normal during chronic HBV infection. Chronic oral steroid use was defined as the use of prednisolone at least 20mg once daily, or 0.5mg/kg/day, whichever dose was lower, for at least 3 months. Low-dose oral steroid use was defined as prednisolone use of 0.5mg/kg/day and less.

The mean age of the subjects was 74.1 years old; 16 were male (64%) and 9 (36%) were female. Fifteen patients had bullous pemphigoid, 4 had endogenous eczema, 2 had pemphigus, 1 had chronic plaque psoriasis, and 1 had chronic actinic dermatitis (Table 1). The mean duration of patients having dermatological disease was 4.0 years. Eighteen patients (72%) had used systemic steroids. The types of non-steroid immunosuppressants used were azathioprine, methotrexate, cyclosporine and rituximab. There were 2 patients on cyclosporine, 6 patients on azathioprine (5 receiving a dose of 50mg daily, and 1 patient on 25mg daily), 2 patients on methotrexate (dosage ranging from 2.5mg once a week to 15mg once a week), and 1 patient was given 2 doses rituximab after being recruited (at the point of recruitment only having received oral prednisolone).

The lowest initial prednisolone dose used was 7.5mg once daily, while the highest initial dose was 30mg once daily (0.5mg/kg/day). The prednisolone doses at the initiation of therapy tended to be low (≤ 0.5 mg/kg/day).

The mean duration of follow-up among 25 patients was 30.8 months. Four patients with chronic HBV infection had detectable HBV DNA on the first visit. All received therapeutic antivirals and had undetectable HBV DNA levels with treatment. The 21 remaining patients had resolved HBV infection; none had detectable HBV DNA at initial assessment. Seven were started on antivirals (6 for prophylaxis and 1 after reactivation occurred). Of the 6 started on prophylactic antivirals, 4 were maintained on high-dose steroids >20 mg/day for at least 4 weeks (range 4–16 weeks), and 2 were

maintained on moderate-dose steroids >10mg/day for at least 4 weeks.

In comparison, of the 14 patients with resolved HBV infection who did not receive prophylactic antivirals, 1 received clobetasol ointment (equivalent to systemic oral steroids),³ 12 received either high/moderate-dose steroids for durations less than 4 weeks, and 1 patient (patient A) received high-dose steroids for 7 weeks and moderate doses for 12 weeks. She had not been given prophylactic antivirals and reactivated after 22 months of chronic steroid therapy.

Due to lower costs, telbivudine (n=5) was the most common antiviral agent used, followed by lamivudine (n=3) and entecavir (n=3). Among the 21 with resolved HBV infection, there were no cases of hepatitis flare.

There were 2 cases of hepatitis B reactivation (Patients A and B). Patient A had used 7 weeks of high-dose steroids at 20mg/day, 12 weeks of moderate- to high-dose steroids (10–20mg/day) in her lifetime, and was on low-dose prednisolone 3mg/day when she reactivated. At that time of reactivation, she had already been on this low maintenance dose for at least 9 months and received 22 months of chronic steroid therapy. She received a total of 20 months telbivudine therapy, but had HBV DNA become undetectable by 4 months of antiviral therapy.

Patient B received 27 months of chronic steroid therapy at the time of reactivation. She demonstrated a reverse seroconversion from HBsAg negative to HBsAg positive. She had used 7 weeks of high-dose steroids at least 20mg/day, 13 weeks of moderate- to high-dose

steroids, and was on low-dose prednisolone 3mg/day when she reactivated (on this low dose for 2 years prior to reactivation). Patient B elected not to receive antivirals. Without antivirals, her HBV DNA levels became undetectable 11 months after the point of detection.

Existing guidelines by major liver societies suggest that patients with chronic HBV infection and patients with resolved HBV infection should be treated similarly.^{2,4-6} Antiviral prophylaxis should be started before and continued well after cessation of immunosuppression, 12 to 18 months if rituximab is used and 6 to 12 months for other immunosuppressive agents.⁷ The European Association for the Study of the Liver and American Association for the Study of Liver Diseases recommend that patients should be continued on biochemical monitoring for hepatitis B reactivation that may occur post-antiviral withdrawal.^{4,5}

The strengths of this study include longitudinal follow-up of patients over at least 4 years with careful surveillance of hepatitis serologies and documentation of their treatment modalities. The exclusion of patients with any underlying cirrhotic disease or pre-existing liver dysfunction mirrors real-world practice where the use of potent immunosuppressant therapy tends to be restricted in such patients.

Our study shows that the majority of patients with moderate-to-severe skin disease with resolved HBV infection remain well without antiviral treatment while on chronic immunosuppression. Nonetheless, patients should be risk-stratified so that those at higher risk of hepatitis B reactivation receive antiviral prophylaxis.

Table 1. Demographics, hepatitis serologies, treatment and surveillance patterns in 25 patients with anti-HBc total positive at first screen

Parameter	Overall (N=25) No. (%)
Demographic	
Mean age at diagnosis, years	74.1 (median 75, range 51–94)
Sex	
Male	16 (64)
Female	9 (36)
Duration of disease	
Mean duration of disease, years	4.0 (median 5, range 1–17)
Indication for treatment	
Bullous pemphigoid	15 (60)
Endogenous eczema/atopic dermatitis	4 (16)
Pemphigus vegetans/oral pemphigus vulgaris	2 (8)
Chronic plaque psoriasis	1 (4)

Table 1. Demographics, hepatitis serologies, treatment and surveillance patterns in 25 patients with anti-HBc total positive at first screen (Cont'd)

Parameter	Overall (N=25) No. (%)
Chronic actinic dermatitis	1 (4)
Asteatotic eczema	2 (8)
Hepatitis serologies at initial assessment	
Anti HBc-total positive	25 (100)
HBsAg positive (chronic HBV infection)	4 (16)
HBsAg negative (resolved HBV infection)	21 (84)
HBV DNA detected (in patients with chronic HBV infection)	4 out of 4 (100)
Laboratory surveillance patterns	
Three-monthly HBV DNA check	17 (68)
Six monthly HBV DNA check	3 (12)
Lost to follow-up/unchecked	5 (20)
ALT normal at diagnosis	24 (96)
ALT abnormal at diagnosis	1 (4)
Number of cases with ALT abnormality during subsequent follow-up	0
Abnormal liver function tests due to HBV reactivation	0
Outcomes	
Number of hepatitis flares	0
Virological suppression with antiviral treatment in patients with chronic HBV infection	4 out of 4 (100)
Reactivation of HBV in patients with resolved HBV infection ^a	2 out of 21 (9.5)
Antiviral therapy	
Number on antivirals	11 (44)
Number of patients with chronic HBV infection on antivirals	4/4 (100)
Number of patients with resolved HBV infection on antivirals	For prophylaxis: 6/21 (33.3%), 1/21 subsequently reactivated and was given antivirals
Telbivudine	5/11 (45.4)
Lamivudine	3/11 (27.3)
Entecavir	3/11 (27.3)
Types of immunosuppressive therapy	
Oral steroid only	18 (including 1 patient with topical clobetasol ointment used) (72%)
Oral steroid + non-steroid immunosuppressants	6 (24)
Non-steroid immunosuppressants only	1 (4)
Types of non-steroid immunosuppressants	
Number of patients who received azathioprine	6
Number of patients who received methotrexate	2
Number of patients who received cyclosporine	2
Number of patients who received rituximab ^b	1

ALT: alanine aminotransferase; HBc: hepatitis B core; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus

^a These 2 patients were not previously on antivirals prior to reactivation^b The patient used rituximab only after recruitment (with inclusion criteria being no previous/concomitant biologic use at time of recruitment)

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