

Letter to the Editor

Rheumatology Advances in Practice 2017;0:1–2
 doi: 10.1093/rap/rkx009
 Advance Access Publication 2 November 2017

Key message

- Iatrogenic HBV reactivation is potentially fatal but preventable by screening prior to starting immunosuppressive therapy.

Comment on: BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs

SIR, we read with great interest the recently published British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guideline by Ledingham *et al.* [1] on the prescription and monitoring of non-biologic DMARDs. We congratulate the BSR Guideline Working Group on their comprehensive work and agree with many of the recommendations. In particular, we are very pleased that routine screening for HBV infection before starting DMARD therapy is now recommended. Reactivation of HBV in patients undergoing immunosuppressive therapy is a well-recognized and potentially fatal complication, yet preventable. We would like to take this opportunity to report a case of HBV reactivation shortly after starting MTX treatment and to emphasize the importance of baseline screening for chronic HBV infection.

A 30-year-old Caucasian male patient was referred with longstanding PsA in May 2017. He had been treated with SSZ in the past but had been without immunosuppression owing to family planning since 2011. On examination, he had active skin psoriasis and polyarthritis. There was no other significant past medical history; he was a non-smoker, consumed alcohol socially and did not use any illicit drugs. He had a long-term female sexual partner. His baseline blood tests, including liver function tests, were unremarkable. He was started on MTX 10 mg once weekly and folic acid 5 mg once weekly. On his 2-week monitoring blood test, his liver function tests were markedly deranged, including alanine aminotransferase (ALT) of 2577 U/l and bilirubin 67 μ mol/l. He developed a transient period of jaundice lasting for 1 week but did not seek medical attention and continued with the MTX. He attended his follow-up rheumatology appointment 4 weeks after starting the MTX, when he was no longer jaundiced, and liver function tests revealed improvement in his ALT at 119 U/l. Further liver investigations, including a viral hepatitis screen, indicated likely reactivation of HBV. His serology showed positive HBsAg, low-titre IgM core antibody, high-titre IgG core antibody (anti-HBc), negative e antigen and positive e antibody, with an HBV DNA viral load of 2.11 log IU/ml.

There is a vast amount of evidence that HBV-induced liver inflammation is, in fact, mainly immune mediated. HBV replication and expression of viral epitopes in infected hepatocytes is followed by a predominantly CD8⁺ T-lymphocyte-induced acute or chronic liver inflammation. In chronic HBV infection, spontaneous intermittent increases in ALT concentrations preceded by an increase in serum HBV DNA are common [2]. Immunosuppressive drugs can trigger these flares, and in particular, CSs can directly stimulate HBV replication. Furthermore, the immunosuppressive effect on the host immune system indirectly leads to abundant viral replication. In addition, sudden withdrawal of immunosuppressive drugs can result in an exaggerated host immune response, leading to potentially life-threatening liver injury [3].

The list of immunosuppressive drugs associated with HBV reactivation has been constantly expanding. The most commonly reported synthetic DMARD associated with HBV reactivation is MTX, although in the majority of cases concomitant use of other immunosuppressive drugs is described. The risk of HBV reactivation by MTX alone is therefore considered to be low, but higher with concomitant use of CSs [4, 5]. Young male patients appear to be at highest risk of reactivation, although the risk mostly depends on HBsAg status [6].

HBV screening standards and the prevention of HBV reactivation have dramatically changed in the past decade. Improved recommendations regarding screening for HBV infection before starting immunosuppressive agents or chemotherapy have been mastered by various gastroenterology societies. The latest one, for example, the 2017 clinical practice guideline by the European Association for the Study of the Liver, includes screening all patients for HBV markers before starting any immunosuppression; and in addition, HBsAg-positive patients should be offered prophylaxis with entecavir or tenofovir, whereas HBsAg-negative anti-HBc-positive subjects should simply be monitored for reactivation rather than receive prophylaxis unless they are at high risk of reactivation [7, 8]. These important risk factors include treatment with rituximab or concomitant CS use. The American Gastroenterological Association considers prednisolone at a dose >10 mg daily (or equivalent) given for >4 weeks as a moderate risk, and recommends antiviral therapy rather than monitoring [8].

The cost of routine HBV screening before immunosuppression and frequent DNA monitoring in core antibody carriers receiving DMARD therapy is an important practical issue. Studies examining the cost-effectiveness of universal screening for HBV infection in Western European rheumatology populations, where the prevalence of HBV infection is low, are lacking. However, routine screening for HBV infection has been shown to be cost-beneficial in lymphoma patients receiving rituximab [9].

In conclusion, the 2017 BSR and BHPR guideline has progressed regarding recommendations for screening for chronic viral hepatitis B infection before starting DMARDs. Compelling evidence supports the routine screening for chronic HBV infection before starting any immunosuppression, and potent prophylactic therapies are available to prevent fatal complications.

Disclosure statement: The authors declared no conflict of interest.

Angela Pakozdi¹ and Hasan Tahir¹

¹*Department of Rheumatology, Whipps Cross University Hospital, Barts Health NHS Trust, London, UK*

Accepted 20 October 2017

Correspondence to: Angela Pakozdi, Barts Health NHS Trust, Rheumatology Department, Whipps Cross Hospital, Whipps Cross Road, London E11 1NR, UK.

E-mail: angela.pakozdi@bartshealth.nhs.uk

References

- 1 Ledingham J, Gullick N, Irving K et al. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. *Rheumatology* 2017;56:865–8.
- 2 Perrillo RP. Acute flares in chronic hepatitis B: the natural and unnatural history of an immunologically mediated liver disease. *Gastroenterology* 2001;120:1009–22.
- 3 Calabrese LH, Zein NN, Vassilopoulos D. Hepatitis B virus (HBV) reactivation with immunosuppressive therapy in rheumatic diseases: assessment and preventive strategies. *Ann Rheum Dis* 2006;65:983–9.
- 4 Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015;148:221–44.e3.
- 5 Fukuda W, Hanyu T, Katayama M et al. Incidence of hepatitis B virus reactivation in patients with resolved infection on immunosuppressive therapy for rheumatic disease: a multicentre, prospective, observational study in Japan. *Ann Rheum Dis* 2017;76:1051–6.
- 6 Lok AS, Liang RH, Chiu EK et al. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. *Gastroenterology* 1991;100:182–8.
- 7 European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017;67:370–98.
- 8 Reddy KR, Beavers KL, Hammond SP et al. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015;148:215–9; quiz e16–7.
- 9 Zurawska U, Hicks LK, Woo G et al. Hepatitis B virus screening before chemotherapy for lymphoma: a cost-effectiveness analysis. *J Clin Oncol* 2012;30:3167–73.