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LETTER TO THE EDITOR

Risk of viral reactivation in patients with occult hepatitis B virus infection during ruxolitinib treatment

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Dear Editor,

Janus kinases (JAKs) are a family of cytoplasmic non-receptor tyrosine kinases (JAK1, JAK2, JAK3, TYK2) associated with cytokine receptors lacking intrinsic kinase activities. Ligand binding to these cytokine receptors activates JAKs, resulting in phosphorylation and homodimerization of signal transducer and activator of transcription (STAT), leading to activation of transcription [1]. JAK1 and JAK3 are associated with the gamma receptor common to receptors of cytokines including interleukins 2, 4, 7, 9, 15, and 21, which play crucial roles in T cell immune responses [1]. JAK2 is associated with the erythropoietin and thrombopoietin receptors [2]. JAK2 gene mutations leading to its constitutive activation are the most common genetic aberration in myeloproliferative neoplasms (MPNs) [2, 3]. Treatment with the JAK 1/2 inhibitor ruxolitinib is highly effective in MPN [3]. However, JAK1 inhibition by ruxolitinib also perturbs the immune response, which is dependent on cytokines and hence JAK/STAT signaling. While these perturbations may be therapeutically exploited, as in treating graft-versus-host-disease [4], they also predispose to infections [5].

People previously infected by hepatitis B virus (HBV) are serologically positive for anti-HBV core antigen antibody (anti-HBc). Subjects who have successfully cleared the virus are negative for HBV surface antigen (HBsAg) and serum HBV DNA. Subjects who still carry the virus are HBsAg-positive. These carriers may in time lose their HBsAg and even serum HBV DNA. However, HBV can still persist as covalently closed circular DNA in the liver, so that viral reactivation and HBV-related complications may occur [6]. Both groups are indistinguishable from each other in routine clinical practice. For practical purposes, subjects anti-HBc-positive, HBsAg-negative, and HBV DNA-negative are considered to have occult HBV infection. With potent B cell depleting immunochemotherapy, viral reactivation might happen in occult HBV infection, with 2-year cumulative rates of 35% in patients with pre-existing anti-HBsAg antibody (anti-HBs) and 68% in those without anti-HBs [7].

In this study, we prospectively evaluated a cohort of MPN patients with occult HBV infection who required treatment with ruxolitinib, in order to define the frequency and time course of viral reactivation.

From January 2016 to December 2017, consecutive MPN patients requiring ruxolitinib therapy were studied. Laboratory evaluations included liver biochemistry, serologic tests for anti-HBc, HBsAg, anti-HBs (Abbot Laboratories, Chicago, IL, USA), and serum HBV DNA (Abbott RealTime HBV DNA assay, Abbott Molecular, Des Plaines, IL; lower limit of detection 10 IU/mL); performed before ruxolitinib treatment, then every 4 weeks for the first 3 months and every 3 months thereafter [5]. The primary endpoint was HBV reactivation, defined as detectable serum HBV DNA (≥ 10 IU/mL), irrespective of transaminases or HBsAg status. The secondary outcomes were serum alanine aminotransferase (ALT) level and HBsAg positivity at reactivation. Patients gave informed consent. The study was approved by the Institutional Review Board of the University of Hong Kong and conducted according to the Declaration of Helsinki.

In the 2-year study period (data censored at December 31, 2017), 40 Chinese MPN patients required ruxolitinib treatment (Supplemental File 1). Three patients were HBsAg-positive and were given anti-HBV prophylaxis (entecavir, 0.5 mg/day). Of the 37 HBsAg-negative patients, 15 were anti-HBc-positive (Table 1). They all had undetectable serum HBV DNA. None had concomitant chronic liver disease due to other viral hepatitis (C, D), primary biliary cholangitis,

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Table 1 Clinicopathologic features of 15 patients with occult hepatitis B virus (HBV) infection and myeloproliferative neoplasms (MPNs) undergoing ruxolitinib treatment

Clinicopathologic features	No HBV reactivation ($N = 11$)	HBV reactivation ($N = 4$)
Gender		
Male	7	3
Female	4	1
Median age (range), years	60.5 (27.3–75.6)	71.0 (51.8–82.3)
MPN diagnosis		
Polycythemia vera (PV)	2	0
Essential thrombocythemia (ET)	2	1
Primary myelofibrosis (MF)	5	1
Post-PV MF	0	0
Post-ET MF	1	1
MPN—unclassifiable	1	1
Blood count before ruxolitinib		
Median hemoglobin (range), g/dL	11.2 (6.8–16.3)	11 (10.8–14.6)
Median white cell count (range), $\times 10^9$/L	9.6 (4.0–37.3)	17.9 (14.5–28.4)
Median platelet count (range), $\times 10^9$/L	512 (120–1206)	446 (169–1500)
Median blast percentage (range)	0 (0–4)	2 (0–4)
Median lactate dehydrogenase (range), U/L	399 (204–1281)	371.5 (140–677)
Molecular status		
JAK2 V617F positive	8	2
CALR mutation positive	1	1
MPL mutation positive	0	1
JAK2, *CALR*, *MPL* mutation negative	2	0
Ruxolitinib dose		
5 mg twice daily	2	1
10 mg twice daily	1	1
15 mg twice daily	4	0
20 mg twice daily	4	1
25 mg twice daily	0	1
Prior hydroxyurea therapy	7	2
Prior pegylated interferon therapy	0	1
Detectable baseline anti-HBs	8	3
Median anti-HBs (range), m.i.u./mL	24 (11–1000)	19 (13–133)
Median follow-up (range), months	19.7 (2.4–24)	12.4 (8.1–22.7)

autoimmune hepatitis, Wilson's disease, or significant alcohol intake (women > 20 g/day; men > 30 g/day). At a medium follow-up of 19.2 (2.4–24.0) months, four patients (26.7%) had HBV reactivation (Supplemental File 2), occurring at a median of 10.5 (6.9–12.8) months after ruxolitinib treatment. The estimated cumulative incidences of HBV reactivation at 6 and 12 months were 7.7 and 30.8% (Fig. 1). The median HBV DNA level at reactivation was 16 (10–32) IU/mL. ALT was elevated in one patient to 107 U/L (reference range 8–58 U/L). None had detectable HBsAg at reactivation. We did not have access to quantification of anti-HBc. However, there were no significant differences in the baseline anti-HBs titers between patients with or without HBV DNA reactivation ($P = 0.73$) (Table 1).

In all four patients, HBV DNA was confirmed to be detectable by a second assay before commencement of anti-viral treatment. They were treated with entecavir (0.5 mg/day), administered at a median of 21 (8–35) days after the first positive HBV DNA assay. All cases had ALT normalizing in 2 weeks, and HBV DNA undetectable in 4 weeks. HBV-related hepatic complications were not observed.

This was the first prospective study of HBV reactivation in patients with occult HBV infection undergoing ruxolitinib therapy. Our monitoring strategy allowed timely and effective treatment with entecavir, thereby preventing clinical hepatitis and HBV-related hepatic complications. Importantly, ruxolitinib could be safely continued without interruption or dose reduction. Interestingly, HBV reactivation occurred

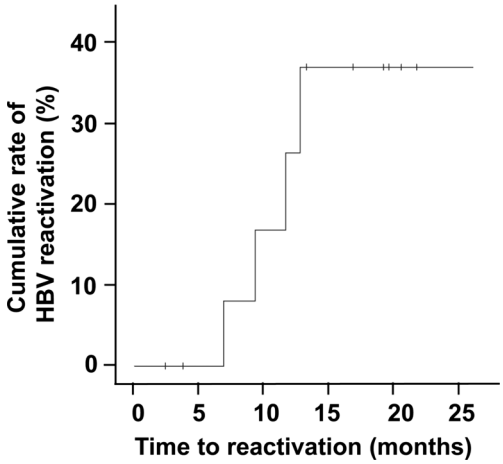

Fig. 1 Cumulative risk of viral reactivation in patients with occult HBV infection undergoing ruxolitinib treatment

despite the presence of anti-HBs in three cases. In patients with occult HBV infection undergoing B cell depleting immunochemotherapy, undetectable anti-HBs was the single-most important risk for HBV reactivation [7]. It is therefore important to note that in ruxolitinib-treated patients, detectable anti-HBs might not be protective regarding HBV reactivation.

Our observations should be interpreted in the context of age and population-specific differences in HBV reactivation [8]. In HBV non-endemic (European, North American) populations, HBV exposure usually occurs during adulthood, resulting in a self-limiting acute infection. HBsAg-negative, anti-HBc-positive subjects in these populations might have actually cleared the virus, so that HBV reactivation rates are low. However, in HBV endemic (Asian, African) populations, HBV infection occurs in perinatal periods and childhood, coinciding with the immune tolerant phase, which ultimately results in a chronic carrier state. HBsAg is later gradually cleared, and seroconversion to an HBsAg-negative state may occur at around the fifth decade of life, although HBV DNA still persists in the liver [8]. MPNs generally also present at the fifth or sixth decade. Hence, HBsAg-negative, anti-HBc-positive MPN patients in HBV-endemic areas are more likely to have persistent occult infection and hence a higher risk of viral reactivation. The high HBV reactivation rate induced by ruxolitinib, observed in our HBsAg-negative, anti-HBc-positive patients from an HBV-endemic population, should therefore be confirmed in HBV non-endemic populations. We also used a very sensitive HBV DNA assay, which might explain in part the higher virologic reactivation rate as compared with previous studies where HBV DNA assay of a lower sensitivity was employed.

Anecdotal reports had shown that ruxolitinib treatment in chronic HBV carriers (HBsAg-positive and/or serum HBV DNA-positive) might lead to viral reactivation [9–12], suggesting that anti-HBV prophylaxis might be beneficial for these patients [13]. In HBsAg-negative individuals, testing for anti-HBc is needed to detect a potential occult carrier state. In HBsAg-negative anti-HBc-positive individuals, our monitoring strategy allows anti-HBV treatment to be restricted to patients with actual HBV reactivation. However, if such monitoring cannot be implemented, anti-HBV prophylaxis may have to be considered for subjects with occult HBV infection receiving ruxolitinib treatment, especially in HBV endemic populations. This is because viral reactivation may lead to overt hepatitis and death from hepatic failure [13]. It is also important to continue virologic monitoring during anti-viral treatment. These approaches are already recommended for subjects with occult HBV infection undergoing rituximab-containing immunochemotherapy and hematopoietic stem cell transplantation [7, 14].

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G. Leung: treated the patients, performed the study, and approved the manuscript.

W.K. Seto: performed the study and approved the manuscript.

Y.L. Kwong: conceived the study, treated the patients, wrote and approved the manuscript.

Compliance with ethical standards

The study was approved by the Institutional Review Board of the University of Hong Kong and conducted according to the Declaration of Helsinki.

Conflict of interest The authors declare that they have no conflict of interest.

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