Baricitinib plus leflunomide: a potentially dangerous combination?

Sirs,

Baricitinib is an oral, reversible Janus Kinase inhibitor (JAKi) that selectively inhibits JAK_1/JAK_2 enzymes, approved in rheumatoid arthritis (RA) patients with moderate-to-severe disease. Previous studies demonstrated: i) acceptable overall safety and efficacy profiles with close monitoring; ii) mild to modest thrombocytosis in small proportions of patients receiving JAKi and iii) that the mechanism of action for development of thromboembolic events in patients on JAKi remains unknown (1-3).

Clonal thrombocytosis is associated with increased risk of thrombohaemorrhagic complications and, over time, could progress to myelofibrosis and acute myeloid leukaemia, as opposed to reactive thrombocytosis (4).

We first noticed persistent modest thrombocytosis and subsequent haemorrhagic complication in our index RA patient after receiving baricitinib (BAR) and concomitant leflunomide (LEF) (Patient 1, Table I). This prompted a retrospective review of medical records and blood parameters of all RA patients who were actively attending our rheumatology service at the University Hospital of Kerry and were on JAKi (either tofacitinib or BAR) and conventional synthethic disease modifying antirheumatic drugs (csDMARD) combination. The focus then shifted to RA patients specifically on BAR-LEF combination.

Five RA patients were identified on the BAR-LEF combination (all females; mean age 58) (Table I). All patients were seropositive (for both rheumatoid factor and anti-cyclic citrullinated peptide); none had baseline thrombocythaemia, splenectomy, iron or B_{12} deficiency, thrombohaemorrhagic history, recent infection or malignancy. Platelet elevation was observed in all patients (two remained within normal platelet range) after concomitant use of BAR (mean increase of $160x10^9$/L); however, none developed extreme thrombocytosis ($\geq$1,000 $x10^9$/L).

Modest thrombocytosis was noted and remained persistent in 3 patients throughout the combination treatment duration (mean peak count of $594.7x10^9$/L; mean increase of $200.7x10^9$/L), including after BAR dose reduction in two patients (from 4mg to 2mg). The index patient (Patient 1, Table I) developed vaginal bleeding 4 months after the combination therapy and required eventual surgical intervention by the gynaecological team. No cause for the bleeding was found despite thorough investigations including negative screening for gynaecology malignancy. The second patient (Patient 2, Table I) developed severe pneumonia 3 months after BAR was added to LEF, with both DMARDs held during hospitalisation. In both patients BAR was subsequently switched to a different DMARD.

Two other patients developed infections within 3-6 months of the combination therapy but did not require hospitalisation; Patient 3 (Table I) developed severe tooth infection within 3 months of therapy requiring tooth extraction and an oral antibiotic course (and has since been on BAR monotherapy) while patient 4 (Table I) developed mild *E. coli* urinary tract infection 6 months post combination therapy, treated with a course of oral antibiotic.

C-reactive protein (CRP) was reduced in all patients to within normal limits (<1mg/dL) with significant improvement of Clinical Disease Activity Index (CDAI) after addition of BAR (but with the exception of patient 2 who initially had CRP suppression with the treatment combination but eventually developed CRP elevation during her hospitalisation with severe pneumonia (Table I). She was also noted to develop early concomitant leukocytosis along with the thrombocytosis after commencement of BAR.

None of the patients with moderate thrombocytosis underwent further diagnostic evaluation such as peripheral blood smear review, cytogenetic or bone marrow analysis. No patient developed venous thromboembolism (VTE) episodes during the duration of treatment; although, all three of patients with moderate thrombocytosis discontinued the combination therapy very early (Patients 1-3, Table I; within 6 months).

All patients involved had complete resolution of adverse events (AEs) including normalisation of platelet count after discontinuation of the combination therapy. Interestingly, patient 5 (Table I) who only had very mild elevation of her platelet count but of normal range remained well throughout (currently 18 months post combination therapy) and her RA remained in remission. No patients developed serious AEs or thrombocytosis on tofacitinib-csDMARD combinations, while for patients on other BAR combinations, despite some patients having mild increase of platelets

Table I. Demographic of seropositive rheumatoid arthritis patients receiving baricitinib and leflunomide.

Patient	Age	Gender	Dose of LEF (mg)	Total cumulative LEF dose prior to BAR (mg)	Baseline platelet count ($x10^9$/L)	CRP prior to BAR addition	Baseline CDAI prior to BAR addition	Peak platelet post BAR addition	CRP post BAR addition	CDAI post BAR addition	CRP post cessation of LEF + BAR combination ***	Platelets post cessation of LEF + BAR***	AEs within 3-6 months BAR addition	Concomitant leukocytosis post BAR addition
1	54	F	20	15,100	418	52	34	645	0.3	3.5	0.8	379	Vaginal bleeding	No
2	59	F	20	22,800	393	17	19.5	524*	0.9*	2	1.0	382	Severe pneumonia	Yes
3	52	F	10**	17,900	371	4.1	16	615	0.5	1	0.5	396	Dental infection	No
4	74	F	10	1,200	229	9.9	19	391	0.5	3	0.5	253	Mild UTI	No
5	51	F	20	3,600	233	6.3	20	269	0.5	1	NA	NA	-	No

LEF: leflunomide; BAR: baricitinib; CRP: C-reactive protein; CDAI: clinical disease activity index; AEs: adverse events; UTI: urinary tract infection; NA: not available (as patient remained on both BAR-LEF combination).
*CRP and peak platelet in patient 2 reflect levels during blood monitoring after commencement of BAR, but prior to her admission with severe pneumonia (Peak CRP and platelet during pneumonia was 139 and 504 respectively).
**Patient 3 developed rash on higher dose of LEF.
*** Patient 1 was on LEF and Benepali, patient 2 on Abatacept and Plaquenil, patient 3 on BAR monotherapy, while patient 4 was on LEF and Benepali during repeat CRP and platelets. Note: The peak platelet count post BAR addition in all patients were not during the course of active infections or active bleeding.

compared to baseline, all levels remained within the normal range and with no serious AEs.

JAK_2 is essential in thrombopoetin signalling and is a primary regulator of platelet regulation; (5) which may partly explain why BAR (and not tofacitinib) may directly impact platelet production. Theoretically, renal organic anion transporter (OAT)-3 inhibitor such as LEF could affect the plasma exposure of BAR; however, dedicated interaction studies between BAR and LEF have not been conducted (6).

The potential interaction between BAR and LEF may be important but not yet recognised. We report 2 cases of serious infections (including 1 of severe pneumonia) and 1 case of significant haemorrhagic episode, all presenting with moderate thrombocytosis occurring within 3-6 months of this combination therapy. An intriguing observation is that these 3 patients had higher LEF cumulative doses when BAR was commenced compared to the other 2 patients. Our report highlights the need for awareness in RA patients receiving BAR and concomitant LEF. All findings occurred within 3 to 6 months of the combination therapy and reversed by discontinuation of either drug.

This study is, however, subject to inherent limitations, particularly that it is a small observational case series. We acknowledge that the bleeding in patient 1 may have been coincidental, which in turn may have worsened the thrombocytosis. Furthermore, RA and DMARDs are both known independent risk factors for infection. However, a high incidence of infections was seen in this series within a short period of time (3 of the 5 patients (60%) and occurred early within 3–6 months of this combination therapy).

We would recommend that caution should be used when BAR and LEF are given concomitantly and consideration should be given to start them at lower doses. Moderate thrombocytosis with concomitant leukocytosis (despite normal CRP) may be an early sign for development of severe infection while isolated moderate thrombocytosis may be an early sign or risk for infection or thrombohaemorrhagic episodes; therefore, these patients should require closer monitoring. Well suppressed CRP in these patients (despite the thrombocytosis) points toward a clonal rather than reactive cause; however, more investigations will be needed while the relevance and possible complications of the thrombocytosis remains unknown. We advocate for future studies of sufficient size to delineate the drug interactions between BAR and LEF and welcome other centres to share their experiences on this regimen therapy.

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References

1. GENOVESE MC, SMOLEN JS, TAKEUCHI T *et al.*: Safety profile of baricitinib for the treatment of rheumatoid arthritis over a median of 3 years of treatment: an updated intergrated safety analysis. *Lancet Rheumatol* 2020; e347-e357.
2. FAVALLI EG, MATUCCI-CERINIC M, SZEKANECZ: The Giants (biologicals) against the Pigmies (small molecules), pros and cons of two different approaches to the disease modifying treatment in rheumatoid arthritis. *Autoimmun Rev* 2020; 19: 102421.
3. DOUGADOS M, VAN DER HEIJDE D, CHEN YC *et al.*: Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis* 2017; 76: 88-95.
4. KUYKENDALL AT, KOMROKJI R: What's in a number? Examining the prognostic and predictive importance of platelet count in patients with essential thrombocythemia. *J Natl Compr Canc Netw* 2020; 18: 1279-84.
5. KORIDE S, NAYAK S, BANFIELD C, PETERSON MC: Evaluating the role of Janus Kinase pathways in platelet homeostasis using a systems modeling approach. *CPT Pharmacometrics Syst Pharmacol* 2019; 8: 478-88.
6. CHOY EHS, MICELI-RICHARD C, GONZALEZ-GAY MA *et al.*: The effect of JAK1/JAK2 inhibition in rheumatoid arthritis: efficacy and safety of baricitinib. *Clin Exp Rheumatol* 2019; 37: 694-704.