Baricitinib plus leflunomide: a potentially dangerous combination?

Sirs, Baricitinib is an oral, reversible Janus Kinase inhibitor (JAKi) that selectively inhibits JAK1/JAK3 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 one of our RA patients, who had been on a BAR-LEF combination (all females; Table I) developed mild thrombocytosis (≤200x10^9/L) but did not require hospitalisation; her platelet count but of normal range (≤450x10^9/L), including from 4mg to 2mg). The index patient (Table 1, Patient 1) 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 1) 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 after 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.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Dose of LEF (mg)</th>
<th>Total cumulative LEF dose prior to BAR (mg)</th>
<th>BAR dose prior to CDAI (mg)</th>
<th>Baseline CRP prior to BAR (mg)</th>
<th>Baseline platelet count (x10^9/L)</th>
<th>Peak platelet BAR addition</th>
<th>CRP post BAR addition</th>
<th>CDAI post BAR addition</th>
<th>CRP post cessation of LEF + BAR combination</th>
<th>Platelets post cessation of LEF + BAR***</th>
<th>AEs within 3-6 months BAR addition</th>
<th>Concomitant leukocytosis post BAR addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>F</td>
<td>20</td>
<td>15,100</td>
<td>418</td>
<td>52</td>
<td>34</td>
<td>645</td>
<td>0.3</td>
<td>3.5</td>
<td>0.8</td>
<td>379</td>
<td>Vaginal bleeding</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>F</td>
<td>20</td>
<td>22,800</td>
<td>393</td>
<td>17</td>
<td>19.5</td>
<td>524*</td>
<td>0.9*</td>
<td>2.0</td>
<td>1.0</td>
<td>382</td>
<td>Severe pneumonia</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>F</td>
<td>10**</td>
<td>17,000</td>
<td>371</td>
<td>4.1</td>
<td>16</td>
<td>615</td>
<td>0.5</td>
<td>1.0</td>
<td>0.5</td>
<td>396</td>
<td>Dental infection</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>F</td>
<td>10</td>
<td>1,200</td>
<td>229</td>
<td>9.9</td>
<td>19</td>
<td>391</td>
<td>0.5</td>
<td>3.0</td>
<td>0.5</td>
<td>253</td>
<td>Mild UTI</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
<td>F</td>
<td>20</td>
<td>3,600</td>
<td>233</td>
<td>6.3</td>
<td>20</td>
<td>269</td>
<td>0.5</td>
<td>1.0</td>
<td>0.5</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
</tr>
</tbody>
</table>

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).

**Patient 3 developed rash on higher dose of LEF.
*** Patient 1 was on LEF and Beneval, patient 2 on Abatacept and Plaquenil, patient 3 on BAR monotherapy, while patient 4 was on LEF and Beneval 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 is essential in thrombopoietin 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 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 leuocytosis (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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Competing interests: none declared.

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References