JAK2 Specificity and Thrombosis Risk: Potential Role of Antiphospholipid Antibodies

To the Editor:

Janus kinase (JAK) inhibitors are a relatively new addition to our tools for treatment of rheumatoid arthritis (RA)[1]. They are responsible for transduction of more than 38 cytokinases[2], with diffuse metabolic/immunologic implications. It is those immunologic effects that have attracted evaluation for modulation as a therapeutic approach to rheumatologic disease[1]. Infection and gastrointestinal perforation, liver abnormalities and serum creatinine, lipid and creatine phosphokinase level elevations may complicate all JAK inhibitors, but thrombotic events appear more limited to baricitinib[3]. Baricitinib has shown efficacy and is approved primarily for the treatment of RA. Not all JAK inhibitors are equal. There are 4 JAK sites[2]. Baricitinib predominantly acts on sites 1 and 2, tofacitinib on sites 1 and 3, filgotinib on site 1, peficitinib on site 3, and upadacitinib on site 1[4,5].

Could baricitinib's JAK2 inhibition (unique among currently investigated JAK inhibitors) be a clue to associated thrombotic events? Baricitinib trials suggest possible increases in thromboembolisms; tofacitinib postmarketing surveillance suggests possible increases in pulmonary thrombosis. According to the publications[3,4,5], the thromboembolic risks are about 5 events per 1000 patient-years with 4 mg baricitinib daily. The general population and controls without RA have 1–4 thromboembolic events per 1000 patient-years. The rates increase in RA to 3–7 per 1000 patient-years.

JAK2 is important in hematologic cytokine induction[5] and mutations are associated with myeloproliferative disease[2]. A possible explanation for thrombotic events with baricitinib may be modulation of platelet function in the presence of a specific risk factor. In a patient with a known autoimmune disease, one must consider an accompanying phenomenon, presence of antiphospholipid antibodies (aPL)[6], especially because involvement of both arterial and venous vessels is rare when aPL are not present[7].

Evaluation for presence of aPL may identify individuals at risk of thrombotic events with baricitinib and perhaps with future agents targeting type 2 JAK sites. The mean prevalence of aPL in patients with RA is 28%, although reports range from 5% to 75%. Curiously, the presence of antiphospholipid or anticardiolipin antibodies (aCL) does not appear to predict the development of thrombosis and/or thrombocytopenia in patients with RA. However, aCL in RA are associated with a higher risk for developing rheumatoid nodules. It is hypothesized that the majority of aCL identified in patients with RA have different specificities than those identified in other diseases that are associated with thrombotic events.

The presence of aPL should at the very least be assessed if thrombotic events develop in a patient receiving a JAK inhibitor, because standard treatment of thrombotic events requires modification in their presence[8,9]. Too few events have occurred with JAK inhibitors to be certain that these risks are significant. Longterm observational studies are needed to quantify the risks accurately and differentiate them from the underlying disease. In the interim, use of aspirin or cyclooxygenase-1–predominant nonsteroidal antiinflammatory agents with assurance of actual reduction of platelet function, unfractionated heparin, or high-dose warfarin (3.0–3.5 INR) is recommended when aPL are identified in patients who develop thromboembolic disease while receiving a JAK inhibitor.

BRUCE M. ROTHSCHILD, MD, Indiana University School of Medicine, Muncie, Indiana; Carnegie Museum - Vertebrate Paleontology, Pittsburgh, Pennsylvania, USA. Address correspondence to Dr. B.M. Rothschild, 789 Bethel Road, Morgantown, West Virginia 26501, USA. E-mail: spondylair@gmail.com

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