

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 cytokines², with diffuse metabolic/immunologic implications. It is those immunologic effects that have attracted evaluation for modulation as a therapeutic approach to rheumatologic disease¹. 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 baricitinib³. Baricitinib has shown efficacy and is approved primarily for the treatment of RA. Not all JAK inhibitors are equal. There are 4 JAK sites². 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 post-marketing 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 induction⁵ and mutations are associated with myeloproliferative disease². 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 present⁷.

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. Long-term 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.

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REFERENCES

1. Keystone EC, Genovese MC, Schlichting DE, de la Torre I, Beattie SD, Rooney TP, et al. Safety and efficacy of baricitinib through 128 weeks in an open-label, long-term extension study in patients with rheumatoid arthritis. *J Rheumatol* 2018;45:14-21.
2. Alicea-Velázquez NL, Boggon TJ. The use of structural biology in Janus kinase targeted drug discovery. *Curr Drug Targets* 2011;12:546-55.
3. Huizinga TW, Kay J, Harigai M, Keystone E, Smolen J, Rosas J, et al. Effects of baricitinib on haematological laboratory parameters in patients with rheumatoid arthritis [abstract]. *Rheumatology* 2018;57 Suppl 3: key075.589.
4. Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, Berclaz PY, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have an inadequate response to methotrexate. *Ann Rheum Dis* 2015;74:333-40.
5. O'Shea JJ. Targeting the Jak/STAT pathway for immunosuppression. *Ann Rheum Dis* 2004;63 Suppl 2:ii67-71.
6. Cohen D, Berger SP, Steup-Beekman GM, Bloemenkamp KW, Bajema IM. Diagnosis and management of the antiphospholipid syndrome. *BMJ* 2010;340:2541.
7. Yalavarthi S, Gould TJ, Rao AN, Mazza LF, Morris AE, Núñez-Alvarez C, et al. Release of neutrophil extracellular traps by neutrophils stimulated with antiphospholipid antibodies: a newly identified mechanism of thrombosis in the antiphospholipid syndrome. *Arthritis Rheumol* 2015;67:2990-3003.
8. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med* 1995; 332:993-7.
9. Rothschild BM. Comparative antiplatelet activity of COX1 NSAIDS versus aspirin, encompassing regimen simplification and gastroprotection: a call for a controlled study. *Reumatismo* 2004;56:89-93.

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