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LETTER TO THE EDITOR

# Comment on "Safety of Janus Kinase Inhibitors in Older Patients: A Focus on the Thromboembolic Risk"

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Dear Editor,

We read with great interest the work of Rajasimhan et al. [1] on the thrombotic risks associated with Janus kinase (JAK) inhibitors. This topic has certainly engendered much discussion in major rheumatology congresses and journals; however, hematologists have long been aware of tyrosine kinase (TYK) proteins and JAK pathways, both as pathogenic factors and as therapeutic targets. The association between these pathways and thrombotic events is exemplified by myeloproliferative neoplasms (MPNs), which mainly affect older patients and are marked by mutations in JAK2 and thromboembolic manifestations [2]. Given the overlap between some autoimmune diseases and MPNs [3], we ask ourselves, if hematologists are treating these thrombophilic diseases with JAK inhibitors (JAKi), should we really be concerned about thrombosis in our older rheumatic patients when we treat them with JAKi?

TYKs belong to a group of protein kinases that assist with the transmission of extracellular signals across the cell membrane (Fig. 1), including vascular endothelial growth factors (VEGFs) and platelet-derived growth factors (PDGFs) [4]. The JAK family (JAK 1, 2, and 3 and TYK2) belongs to the group of non-receptor TYKs (nr-TYKs) and can dock more than one receptor molecule. As such, JAKi are used in different clinical situations and can have pleiotropic and even antagonistic effects, including thrombogenesis.

The JAKi have different affinities for different JAK enzymes. Tofacitinib is selective for JAK1 and 3, with less activity against JAK2 and TYK2; baricitinib is selective for JAK1 and 2, with moderate activity against TYK2 and significantly less activity against JAK3; and upadacitinib is selective for the JAK1 enzyme [5]. From the hematology perspective, the JAKi ruxolitinib, used to treat MPNs, is selective for JAK1 and 2. Away from the JAK pathway but still under the umbrella of TYK proteins, Abelson-TYK inhibitors (e.g., imatinib) are used to treat chronic myeloid leukemia (CML). Despite being drugs with action at different points of the TYK cascade, thrombotic adverse events secondary to their inhibitory action have been identified in specialties including oncology, hematology [6], and now rheumatology [7].

Hematology studies have suggested that the greater the allele load of mutant JAK2, the greater the risk of thrombotic and cardiovascular diseases in MPNs. The means by which these neoplasms promote thrombosis vary and include increased viscosity via proliferation of hematocrit, platelets, and leukocytes, and greater adhesion between platelets and the endothelium [2]. We intuitively infer that inhibiting this pathway would reduce thrombosis. Despite the heterogeneity of studies and the lack of robust evidence, this impression has been reinforced by different studies, including a recent meta-analysis [6], indicating reduced thrombotic risk with ruxolitinib in patients with polycythemia vera and

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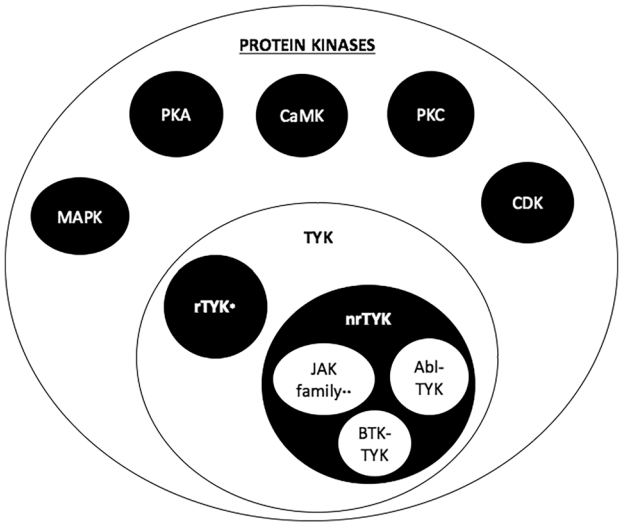


**Fig. 1** Summary of the protein kinase family. "Single asterisk" rTYK are transmembrane proteins that mediate intracellular and extracellular contact, being responsible for, among other functions, binding to growth factors such as vascular endothelial and platelet-derived growth factors. "Double asterisk" JAK family is part of the intracellular JAK-STAT system for transducing a wide array of cytokine signals. Most small-molecule kinase inhibitors recently approved or under development in rheumatology act primarily on this pathway. *Abl-TYK* Abelson tyrosine kinases, *BTK* Bruton's tyrosine kinase (also known as agammaglobulinemia TYK), *CaMK* Ca2+/calmodulin-dependent protein kinase, *CDKs* cyclin-dependent kinases, *JAK* Janus kinase, *JAK-STAT* Janus kinase (JAK)-signal transducer and activator of transcription, *MAPK* mitogen-activated protein kinases, *nr-TYK* non-receptor tyrosine kinases, *PKA* protein kinase A, *r-TYK* receptor tyrosine kinases, *TYK* tyrosine kinases

myelofibrosis [8]. In contrast, the use of new-generation Abelson-TYK inhibitors, such as ponatinib for CML, has been associated with major cardiovascular events as well as dyslipidemia and hyperglycemia. Therefore, the risk of thrombotic events in onco-hematology seems to be more related to some drugs that inhibit different TYK proteins [8, 9]. Given this, it is pertinent for rheumatologists to ask themselves whether the approved JAKi could have different thrombotic risks according to a possible greater or lower affinity with specific signaling pathways of this broad TYK family.

When the US FDA and European Medicines Administration warned about thromboembolic risks with baricitinib, doubt was also cast on the safety profiles of tofacitinib, ruxolitinib, and upadacitinib. Understanding the reasons for the alert is fundamental since this topic caused much uncertainty. This is what the review of the FDA's Adverse Event Reporting System cited by Rajasimhan et al. [1] meant when it warned of possible confounding effects [10]. Regulatory agency alerts are based on fragile evidence; detailed analysis indicated that the thromboembolic events occurred in people with other risk factors for thrombosis, such as higher body mass index, older age and a previous history of venous thromboembolism/deep vein thrombosis [7, 11]. It is essential that rheumatologists and geriatricians deepen their knowledge beyond the JAK pathway and understand that it is part of a broader structure of TYKs. Understanding the interactions between receptor TYK, VEGF, PDGF, and intracellular nr-TYK will allow greater predictability of adverse events and the development of drugs with more specific and potentially less toxic targets.

Even if it seems illogical for JAKi to cause thrombosis from the hematology perspective, other targets of TYK inhibition indicate more thrombotic risk. For now, we agree that the use of JAKi should be avoided in patients at high thromboembolic risk, as suggested by Mease et al. [7]. Even though smoke can come from dry ice, it more commonly indicates fire. So, prudence requires vigilance.

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