Vasculitis induced by Janus kinase inhibitors: truth or illusion?

Sirs,

The JAK/STAT signalling pathway has now emerged as a potential target for the treatment of a variety of autoimmune diseases, such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, Behçet's disease, large-vessel vasculitis and other inflammatory diseases (1-3). In this delightful moment, it is surprising that Janus kinase (JAK) inhibitors not only treat vasculitis but there have been reports of vasculitis induced after its use (4-6). This rare phenomenon is of great concern to us as we are often concerned about the side effects of JAK inhibitors for infections, cardiovascular diseases, malignancies, and thrombotic events.

We conducted a systematic literature review at PubMed up to and including November 01, 2022. We used a combination of the following terms: "Ruxolitinib", "Tofacitinib", "Baricitinib", "Peficitinib", "Delgocitinib", "Upadacitinib", "Fedratinib", "Abrocitinib", "JAK" and "Vasculitis", and excluded articles for which the full-text content was not available, duplicate publications, or that were not relevant to the topic (Fig. 1). The literature search yielded 70 articles after eliminating duplicates. After screening the titles and abstracts and the references of the included papers, three articles were found to be relevant. The eligible articles included a total of 3 case reports (4-6). A total of 3 patients were identified with a male/female ratio of 0/3 and a mean age of 64.7 years (range 52–75) (Table I). Vasculitis induced by JAK inhibitors includes ANCA-associated vasculitis, leukocytoclastic vasculitis, and IgA vasculitis, which are all small-vessel vasculitis. The JAK inhibitors included Tofacitinib (JAK1, 2) and Ruxolitinib (JAK1, 2), which all act on the JAK1 and JAK2 targets. All patients presented with common manifestations of vasculitis, such as acutely worsening renal function and proteinuria in the nephrotic range, necrotising skin lesions of the lower extremities, and purpura. Asemota *et al*. reported a patient who tested negative for p-ANCA prior to treatment with tofacitinib and subsequently tested positive for p-ANCA after treatment with tofacitinib and had biopsy-confirmed ANCA-vasculitis disease (4). The patient reported by Tığlıoğlu *et al*. was not found to have any other factors that could lead to leukocytoclastic vasculitis other than the use of ruxolitinib. In addition, skin lesions appeared after initiation of the drug, subsided after stopping it, and recurred after resuming it, indicating leukocytoclastic vasculitis caused by ruxolitinib, which was then confirmed by skin biopsy (5). Itoh reported a patient who developed IgA vasculitis after 6 months of tofacitinib and skin and kidney biopsy specimens were compatible with IgA vasculitis and demonstrated that this IgA vasculitis was not an adverse effect induced by an allergic reaction (6). The main tools for confirming the diagnosis include skin and kidney biopsies to detect the presence of vasculitis. Pharmacological treatment included discontinuation of JAK inhibitors, steroid hormones, and rituximab.

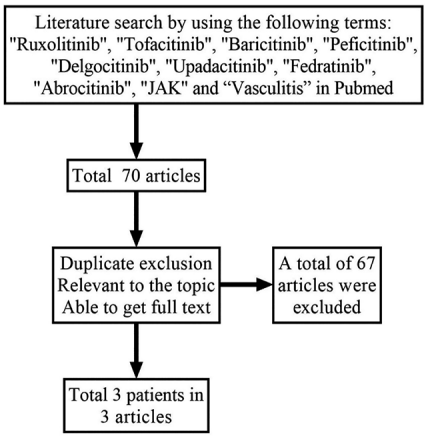

Fig. 1. Flow diagram of the study selection process.

In the articles that mentioned treatment outcomes, 2/3 of the patients had a good prognosis and one patient died of bacterial infections and sepsis.

The sequence of drug administration and vasculitis occurrence in the 3 patients and the final biopsy results revealed that vasculitis caused by JAK inhibitors is explainable. We made a bold conjecture from the above results that biologics targeting JAK1 and JAK2 in the treatment of overactive immune system diseases can induce the development of small-vessel vasculitis under certain trigger conditions, with lesions mainly involving the kidney and skin, and clinical manifestations mainly including abnormal renal function (elevated creatinine, proteinuria) and skin lesions. However, the mechanism of this trigger is unclear. The current knowledge suggests that inhibition of JAK1 and JAK2 targets is followed by inhibition of upstream inflammatory signals (*e.g*. IFN-γ, IL-10, IL-16, IL-23), and that blockade of these cytokines can lead to an imbalance in the immune system, which in turn induces vasculitis (1, 7). However, this explanation is very far-fetched, as only 3 case reports are negligible compared to clinical trials in large real-world populations. The possibility that different individuals have different sensitivities to drugs, as well as the genetic predisposition of patients, cannot be ignored.

However, these "paradoxical" reactions are not only restricted to Jak inhibitors but are also seen in other targeted drugs. For example, adalimumab, a humanised monoclonal antibody that blocks tumour necrosis factor (TNF)-α activity, is licensed for the treatment of psoriasis and other inflammatory diseases. However, several cases of paradoxical psoriasis and erythema-like eruption have been reported following treatment with adalimumab (8, 9). Secukinumab, an anti-interleukin (IL)-17A IgG1-κ monoclonal antibody, is approved for use in psoriasis, psoriatic arthritis, and ankylosing spondylitis. However, rare side effects of IL-17

Table I. General clinical characteristics of three patients with vasculitis induced by the treatment with JAK inhibitors.

	Sex/ Age	JAK inhibitors	Dose	Time 1	Time 2	Types of vasculitis	Disease	Previous treatment	Clinical manifestations	Confirmation examinations	ANCA	Treatment	Prognosis
1 [4]	F/75	Tofacitinib (JAK1, 2)	Not mentioned	2 months	2 months	ANCA-associated vasculitis	Refractory rheumatoid arthritis	Adalimumab, etanercept, prednisone	Acute worsening of renal function and nephrotic-range proteinuria	Kidney biopsy	p-ANCA	Pulse dose steroids, rituximab	Died
2 [5]	F/52	Ruxolitinib (JAK1, 2)	15mg × 2	Not mentioned	Not mentioned	Leukocytoclastic vasculitis	Primary myelofibrosis	Hydroxyurea	Necrotising lesion on a hyperemic background on the posterior of the left ankle	Skin puncture biopsy	/	Discontinued ruxolitinib	Recovered
3 [6]	F/67	Tofacitinib (JAK1, 2)	Not mentioned	6 months	6 months	IgA vasculitis	Rheumatoid arthritis	Famotidine, amlodipine besilate, pregabalin	Proteinuria and purpura of the lower extremities	Skin and kidney biopsy	Negative	Methylprednisolone pulse therapy	Recovered

F: female; Time 1: the time between the onset of use of JAK inhibitors and the appearance of vasculitis; Time 2: the duration of use of JAK inhibitors.

pathway inhibition such as paradoxical psoriasis and atopic-like eczema associated with dermatological manifestations have been already described (10). Rituximab, a genetically engineered chimeric murine/human monoclonal antibody that targets CD20, a B-cell specific surface antigen, is recommended for the treatment of hematologic malignancies, systemic lupus erythematosus, rheumatoid arthritis, microscopic polyangiitis, granulomatosis with polyangiitis and pemphigus vulgaris; however, paradoxical phenomena such as its induction of vasculitis and worsening of pemphigus vulgaris have also been reported (11, 12). Tocilizumab, a humanised anti-human interleukin (IL)-6 receptor antibody, is recommended for the treatment of moderately to severely active rheumatoid arthritis, Castleman disease, adult-onset Still's disease, and systemic juvenile idiopathic arthritis. Like anti-TNFα, rituximab, and abatacept, tocilizumab can induce paradoxical cutaneous eruption such as psoriasis and vasculitis in rare cases (13, 14). However, as previously reported in the literature, these biologically targeted agents may be triggers for paradoxical phenomena found in populations with specific genetic backgrounds. The many examples above highlight the immunological complexities that may surround auto-inflammatory diseases and show the potential double pathophysiological face of biologic agent therapy, which requires extensive attention. In conclusion, we must not only focus on the light side of the moon, but also on its dark side.

This article focuses on the interesting phenomenon that JAK inhibitors can be used to treat an overactive immune system, but in some patients, it also induces another disease of the immune system. The limitation of this article is that there are only 3 cases, which is not enough to elucidate the clinical features of this disease, and publication bias needs to be considered, so there may be more cases in reality, but it reminds clinicians of this rare paradoxical phenomenon. Further research is needed in the future regarding the specific mechanism of how JAK inhibitors lead to the development of vasculitis. Meanwhile, as more and more evidence suggest an association between JAK inhibitors and the induction of vasculitis, a randomised controlled trial is necessary to confirm the clear causality.

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References

1. BANERJEE S, BIEHL A, GADINA M, HASNI S, SCHWARTZ DM: JAK-STAT Signaling as a target for inflammatory and autoimmune diseases: current and future prospects. *Drugs* 2017; 77(5): 521-46. https://doi.org/10.1007/s40265-017-0701-9
2. ZHAO N, TANG Y, WANG S *et al*.: Case report: Refractory intestinal Behçet's syndrome successfully treated with tofacitinib: A report of four cases. *Front Immunol* 2022; 13: 981502. https://doi.org/10.3389/fimmu.2022.981502
3. KOSTER MJ, CROWSON CS, GIBLON RE *et al*.: Baricitinib for relapsing giant cell arteritis: a prospective open-label 52-week pilot study. *Ann Rheum Dis* 2022; 81(6): 861-7. https://doi.org/10.1136/annrheumdis-2021-221961
4. ASEMOTA U, GREENBERG S, GULATI A, KUMAR K, JANGA K: Tofacitinib-induced antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis with crescentic glomerulonephritis. *Cureus* 2021; 13(10): e18663. https://doi.org/10.7759/cureus.18663
5. TIĞLIOĞLU M, TIĞLIOĞLU P, YILDIZ A *et al*.: Leukocytoclastic vasculitis due to ruxolitinib treatment: A rare adverse effect. *J Clin Pharm Ther* 2022; 47(4): 544-7. https://doi.org/10.1111/jcpt.13512
6. ITOH I, KASUNO K, YAMAMOTO C *et al*.: IgA vasculitis developed as an adverse effect of tofacitinib taken for rheumatoid arthritis. *Intern Med* 2020; 59(6): 817-21. https://doi.org/10.2169/internalmedicine.3668-19
7. HU X, LI J, FU M, ZHAO X, WANG W: The JAK/STAT signaling pathway: from bench to clinic. *Signal Transduct Target Ther* 2021; 6(1): 402. https://doi.org/10.1038/s41392-021-00791-1
8. LIN S, QIU X, HONG Y, WANG X, REN J: Necrolytic migratory erythema-like eruption and paradoxical psoriasis associated with adalimumab treatment. *J Dermatol* 2021; 48(11): e572-e3. https://doi.org/10.1111/1346-8138.16140
9. BHADRESHA S, HUGHES AJ, McMAHON L, REEKEN S, NATKUNARAJAH N: Fixed drug eruption secondary to adalimumab. *Clin Exp Dermatol* 2021; 46(2): 366-8. https://doi.org/10.1111/ced.14400
10. MESSINA F, PIASERICO S: The dark side of the moon: the immune-mediated adverse events of IL-17A/IL-17R inhibition. *J Dermatolog Treat* 2022; 33(5): 2443-54. https://doi.org/10.1080/09546634.2022.2062281
11. ABE K, ITOH M, ASAHINA A: Rituximab-induced vasculitis: Does the immune complex of rituximab play a key role in developing paradoxical adverse events? *J Dermatol* 2019; 46(9): e311-e2. https://doi.org/10.1111/1346-8138.14872
12. FELDMAN RJ: Paradoxical worsening of pemphigus vulgaris following rituximab therapy. *Br J Dermatol* 2015; 173(3): 858-9. https://doi.org/10.1111/bjd.13823
13. SPARSA L, AFIF N, BULARCA S *et al*.: [Paradoxical cutaneous reactions associated with tocilizumab therapy]. *Rev Med Interne* 2014; 35(9): 613-6. https://doi.org/10.1016/j.revmed.2014.01.007
14. TERREAUX W, MASSON C, ESCHARD JP *et al*.: Incidence of paradoxical reactions in patients treated with tocilizumab for rheumatoid arthritis: Data from the French registry REGATE. *Joint Bone Spine* 2018; 85(1): 53-7. https://doi.org/10.1016/j.jbspin.2017.01.002