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JANUS KINASE INHIBITORS IN THE TREATMENT OF SYSTEMIC VASCULITIDES

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Abstract

Glucocorticoids (GCs) are still the mainstay of treatment in systemic vasculitides. Immunosuppressive agents such as cyclophosphamide, rituximab, azathiopurine, and mycophenolate mofetil are chosen as steroid sparing agents according to the type of vasculitis. Biologic treatments such as tumor necrosis factor inhibitors and tocilizumab are used in particularly large vessel vasculitis (LVVs) for refractory patients. Janus kinase (JAK)-signal transduction activator of transcription (STAT) pathway activation is involved in the pathogenesis of several inflammatory diseases. JAK inhibitors were also approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis, and ulcerative colitis. However, there are very limited data including mostly case series and open studies with JAK inhibitor usage in systemic vasculitides. Current data mostly come from LVVs and some from Behçet's disease. In the light of current data, we are quite far from suggesting the common usage of JAK inhibitors in systemic vasculitides. JAK/STAT pathway inhibition also may cause severe complications in these group of patients treated with higher dose GC and more potent immunosuppressives compared to RA and ankylosing spondylitis. Although we have limited data showing the efficacy of the JAK inhibitors for systemic vasculitis treatment, they may be used in patients refractory to standard immunosuppresives. JAK inhibitors seem to be promising therapeutic agents, especially for treating LWs. There are ongoing controlled studies with tofacitinib and upadacitinib in TAK; upadacitinib and baricitinib in giant cell arteritis. Larger and controlled studies will clarify the efficacy and safety of JAK inhibitors in the treatment of systemic vasculitides.

Keywords: JAK inhibitors, treatment, vasculitis

INTRODUCTION

Vasculitides are chronic systemic inflammatory diseases characterized by inflammation of the blood vessel wall. The etiopathogenesis of vasculitis is poorly understood. Among different classification efforts, definition according to the involved vessel size is still the most widely accepted and used one (1). Other than involved vessel size, systemic vasculitis also differ in terms of epidemiology, clinical manifestations, treatment, and prognosis. Glucocorticoids are still the mainstay of treatment for systemic vasculitis. Immunosuppressive agents such as cyclophosphamide, rituximab, azathiopurine, and mycophenolate mofetil are chosen as steroid-sparing agents according to the vasculitis type. Biologic treatments, such as tumor necrosis factor inhibitors (TNFi) and tocilizumab, are used, especially in large vessel vasculitis (LVVs) for refractory patients.

Cytokine receptors are divided into several superfamilies according to their shared structural elements (2). Janus kinase (JAK) and signal transduction activator of transcription (STAT) are the main players of a cellular transduction pathway named JAK/STAT. The JAK/STAT pathway is an important pathway involved

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in intracellular signal transduction. Type I and II cytokines use this pathway. They are involved in many physiological and pathological processes. JAKs are members of the intracellular non-receptor protein tyrosine kinase family, and they are able to transfer a phosphate residue from adenosine triphosphate to another substrate. When binding to their membrane receptors, they are activated and phosphorylate STATs to form a phosphorylated (p)-STAT dimer that is capable of migrating into the nucleus and inducing DNA transcription. Four JAKs and seven STATs were identified. Different combinations among these isoforms of the JAK/STAT pathway determine the specificity of signal transduction. Many pro- and anti-inflammatory mediators [interleukin (IL)-2, IL-6, IL-21, IL-12, IL-35, interferon (IFN)-α, IFN-γ, IL-22, IL-10] and growth factors such as erythropoietin, granulocyte-colony stimulating factor, and granulocyte-monocyte-colony stimulating factorsignal through the JAK/STAT pathway (3). JAK/STAT pathway activation is involved in the pathogenesis of several inflammatory diseases. JAK inhibitors (JAKi) have also been approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. Currently used JAKi are not selective for one specific isoform and mostly bind with different affinities to one or more subtypes. Different grades of affinity to different subtypes cause the lack of sensitivity and most frequent adverse effects such as cytopenia as a cause of JAK2 inhibition (2). Data supporting the role of the JAK/STAT pathway in vasculitis pathogenesis, the use of JAKi in systemic vasculitis are mostly focused on LVVs and Behçet's Disease (BD). In this review, we aimed to summarize the data of JAK inhibitor usage for treating systemic vasculitis.

Large Vessel Vasculitis

Giant cell arteritis (GCA) and Takayasu arteritis (TAK) are the main types of LVVs and are characterized by chronic granulomatous inflammation of the vessel wall (4). The pathophysiology of LVVs is poorly understood. However, Th1 and Th17 immune-mediated responses and an imbalance between Th17 and regulatory T (Treg) cells have been previously shown in LVVs. IFN-γ and IL-17 derived from Th1 and Th17 cells are the dominant cytokines (5-9). While $CD4^+$ T cells and macrophages are dominant in granulomatous lesions of GCA, $CD8^+$ T and natural killer cells are also involved in TAK (7). In GCA pathogenesis, most involved cytokines, such as IL-6, IL-12, IFN-γ, IL-17, and IL-23, signal via the JAK-STAT pathway (10). High levels of STAT1 expression were also shown in histopathological with experimentally induced vasculitis model of human temporal arteries grafted in immunodeficient mice (11). In another experimentally induced vasculitis model of GCA, STAT1 and STAT2-dependent target genes were found to be strongly upregulated, and tofacitinib (TOF) prevented adventitial microvascular angiogenesis, decreased hyperplastic intima outgrowth, and tissue-resident memory T-cells (12). In light of these data, it may be hypothesized that their pivotal role in TAK is also another LVVs.

There are only case reports and open studies showing the efficacy of JAKi in LVVs treatment. Li et al. (13) reported 5 refractory TAK patients treated with TOF. Four of the five patients responded well, and acute phase reactants were normalized. No adverse events were reported in the study. Régnier et al. (14) reported the efficacy of baricitinib in 2 patients and ruxolitinib in 1 patient with TAK. Baricitinib was reported as effective in a patient with refractory LVVs (including biologics) overlapping features of TAK and GCA (15). In a recent systematic review, 8 case reports of TAK patients treated with TOF were reviewed. Clinical response and normalization of acute phase response were achieved in 5 of 8 patients.

Angiography had been performed in 4 patients, and reported stable in all. Glucocorticoid dose could be decreased in 6 of 6 patients having the clinical data (16). In a prospective cohort including 53 active TAK patients, TOF and methotrexate (MTX) treatment were compared during follow-up period of 12 months. TOF was found superior to MTX for the achievement of complete remission, prevention of relapse, and tapering of the glucocorticoid dosage (17). In a recent open prospective study, the efficacy and safety of leflunomide (n=35) versus TOF (n=32) were compared in 67 active TAK patients. The observation period was 12 months. Leflunomide and TOF were found to be comparable regarding achieving remission, relapse rate, decrease in acute phase response, and GC dosage in TAK (18).

Sanada et al. (19) reported that upadacitinib was effective in patients with GCA and suggested that it may be a promising agent for remission induction and maintenance therapy in GCA. There are very few case reports with barrictinib reporting efficacy in refractory GCA patients (15,20). A recent Swedish case series including 15 GCA patients (14 baricitinib, 1 TOF) presented the real-life experience of JAKi treatment. All patients were unresponsive to glucocorticoid therapy alone or inappropriate for IL-6-blocking treatment. JAKi were well tolerated without any safety signals, and all patients remained on JAKi for ≥6 months. The mean duration of treatment was 19 months. Significant decreases in C-reactive protein levels and daily glucocorticoid dosage were found after JAKi treatment (21). Koster et al. (22) reported a prospective, open-label, pilot study of baricitinib in 15 GCA patients with a median of 1 (1-2) prior relapse. Fourteen patients completed 52 weeks of baricitinibtherapy. At the end of the study duration, 14/15 (93%) patients had ≥1 adverse event. The most frequent adverse event was infection not requiring

antibiotics (n=8). One patient discontinued baricitinib because of an adverse event. Only 1 of 14 (7%) patients experienced relapse during the study. The remaining patients discontinued glucocorticoid treatment and achieved remission during the study duration (22).

Behçet's Disease

Tulunay et al. (23) reported that the JAK1/STAT3 signaling pathway is activated in BD, possibly through the activation of Th1/Th17-type cytokines such as IL-2, IFN-γ, IL-6, IL-17, and IL-23. In a recent multi-ethnic GWAS study, *IFN-γ receptor-1 (IFNGR1)* gene was shown to be a susceptibility locus for BD (24). IFNGR1 encodes the binding subunit of the IFN-γ receptor, and the binding of IFN-γ stimulates the activation of the JAK-STAT pathway (24).

Transcriptome analysis also showed that Th17-related genes and type I IFN-inducible genes were upregulated and JAK/STAT signaling was activated through Th1/Th17 cytokines in patients with BD (25).

For severe and/or refractory BD, TNF-alpha inhibitors are suggested beyond glucocorticoids and immunosuppressant (26). However, there is still a subgroup of refractory BD patients unresponsive to TNFi. There are some data showing that JAKi may be promising agents, especially in this group of patients. In a case series with 13 (seven male and six female) patients, the efficacy and safety of TOF in refractory BD were recently reported. There were patients with active vascular/cardiac (n=5), gastrointestinal (n=6) and articular (n=2) involvements in this study. After a median follow-up of 8 (5.5-19) months, patients with cardiovascular and articular involvement achieved both clinical and radiological remission. The erythrocyte sedimentation rate and C-reactive protein level significantly decreased. However, among patients with gastrointestinal involvement, intestinal ulceration healed in one patient and persisted in 5 patients. This study reported that active BD patients with vascular and articular involvement responded well to TOF without any safety signal. However, active BD patients with gastrointestinal involvement responded poorly to TOF treatment (27).

Small Vessel Vasculitis

Granulomatosis with polyangiitis, microscopic polyangiitis (MPA), and eosinophilic granulomatosis polyangiitis (EGPA) are the anti-neutrophil cytoplasm antibody-associated vasculitides (AAV). AAVs are necrotizing small vessel vasculitis characterized by pulmonorenal involvement, ocular, ears-nose-throat, skin, gastrointestinal, and neurological involvement. It was previously shown that T cells and associated cytokines such as IL-6, IL-10, IL-12, IL-23, and type I IFNs play an important role in AAV pathogenesis via JAK/STAT pathway activation (28,29). Imatinib mesylate, which is a tyrosine kinase inhibitor, was recently reported to be effective in the treatment of a case with EGPA (30). Recently, a case series including 10 patients with AAV (6 with GPA, 3 with MPA and 1 with EGPA) reported the efficacy and safety of TOF. Complete remission was achieved in 9 of 10 patients. One patient achieved partial remission. There was no relapse during the follow-up of a median of 9.5 months. TOF was found effective in non-organ-threatening AAV patients without any safety signal (31).

Medium Vessel Vasculitis

There are very few data on the use of JAKi in medium vessel vasculitis treatment. Rimar et al. (32) reported a case with systemic polyarteritis nodosum (PAN) treated effectively with TOF in 2016. Zhu et al. (33) reported a refractory cutaneous PAN patient who responded well to TOF. Roy et al. (34) recently reported 4 cases with cutaneous PAN. In this report, 2 of 4 cases used TOF as the primary therapy without glucocorticoids after diagnosis. Remission was achieved in all four patients.

CONCLUSION

Because the JAK/STAT pathway is involved in most of the inflammatory processes in rheumatologic diseases, it is not surprising that JAKi may be effective in patients with refractory vasculitis. However, there are very limited data, including mostly case series and open studies with JAKi usage in systemic vasculitis. Current data mostly comes from LWs and some from. In the light of current data, we are quite far from suggesting the common usage of JAKi in systemic vasculitides. JAK/STAT pathway inhibition can cause severe complications in this group of patients treated with higher dose glucocorticoid and more potent immunosuppressives compared with RA and ankylosing spondylitis. The serious infection risk with JAKi is similar to that with TNFi. However, serious infection risk and herpes zoster development risk are higher with TOF than with TNFi. JAKi use ≥1 year was reported to be associated with increased venous thromboembolism (35). The increase in venous thrombosis risk should be kept in mind while managing patients with BD, which mainly involves venous vessels and leads to venous thrombosis. Surprisingly, there are few case reports of vasculitis induced after JAKi usage. Vasculitis developed after TOF usage in 2 cases and after ruxolitinib, which targets JAK1 and JAK2 (36-38). However, further research and more evidence are needed to assess whether there is a clear causality between vasculitis development and JAKi usage.

Although we have limited data showing the efficacy of JAKi for systemic vasculitis treatment, they may be used in patients refractory to standard immunosuppressives. JAKi appear to be promising therapeutic agents, especially for treating LWs. There are ongoing controlled studies with TOF and upadacitinib in TAK andupadacitinib and baricitinib in GCA. Larger and controlled studies will clarify the efficacy and safety of JAKi in the treatment of systemic vasculitis.

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REFERENCES

1. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65:1-11.
2. Schwartz DM, Bonelli M, Gadina M, et al. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. Nat Rev Rheumatol. 2016;12:25-36.
3. Bursi R, Cafaro G, Perricone C, et al. Contribution of janus-kinase/signal transduction activator of transcription pathway in the pathogenesis of vasculitis: a possible treatment target in the upcoming future. Front Pharmacol. 2021;12:635663.
4. Alibaz-Oner F, Direskeneli H. Update on Takayasu's arteritis. Presse Med. 2015;44:e259-65.
5. Samson M, Audia S, Fraszczak J, et al. Th1 and Th17 lymphocytes expressing CD161 are implicated in giant cell arteritis and polymyalgia rheumatica pathogenesis. Arthritis Rheum. 2012;64:3788-98.
6. Saadoun D, Garrido M, Comarmond C, et al. Th1 and Th17 cytokines drive inflammation in Takayasu arteritis. Arthritis Rheumatol. 2015;67:1353-60.
7. Watanabe R, Berry GJ, Liang DH, et al. Pathogenesis of giant cell arteritis and Takayasu arteritis-similarities and differences. Curr Rheumatol. Rep 2020;22:68.
8. Matsumoto K, Suzuki K, Yoshida H, et al. Longitudinal monitoring of circulating immune cell phenotypes in large vessel vasculitis. Autoimmun Rev. 2022;21:103160.
9. Weyand CM, Goronzy JJ. Immune mechanisms in medium and large-vessel vasculitis. Nat Rev Rheumatol. 2013;9:731-40.
10. Samson M, Corbera-Bellalta M, Audia S, et al. Recent advances in our understanding of giant cell arteritis pathogenesis. Autoimmun Rev. 2017;16:833-44.
11. Deng J, Younge BR, Olshen RA, et al. Th17 and Th1 T-cell responses in giant cell arteritis. Circulation. 2010;121:906-15.
12. Zhang H, Watanabe R, Berry GJ, et al. Inhibition of JAK-STAT signaling suppresses pathogenic immune responses in medium and large vessel vasculitis. Circulation. 2018;137:1934-48.
13. Li J, Li M, Tian X, Zeng X. Tofacitinib in patients with refractory Takayasu's arteritis. Rheumatology. 2020;59:e95-e8.
14. Régnier P, Le Joncour A, Maciejewski-Duval A, et al. Targeting JAK/STAT pathway in Takayasu's arteritis. Ann Rheum Dis. 2020;79:951-9.
15. Régent A, Terrier B, Legendre P, et al. Efficacy of baricitinib for refractory large-vessel vasculitis. Rheumatology. 2021;60:e389-e91.
16. Rathore U, Thakare DR, Patro P, et al. A systematic review of clinical and preclinical evidences for Janus kinase inhibitors in large vessel vasculitis. Clin Rheumatol. 2022;41:33-44.
17. Kong X, Sun Y, Dai X, et al. Treatment efficacy and safety of tofacitinib versus methotrexate in Takayasu arteritis: a prospective observational study. Ann Rheum Dis. 2022;81:117-23.
18. Wang J, Dai X, Ma L, et al. Efficacy and safety of tofacitinib versus leflunomide with glucocorticoids treatment in Takayasu arteritis: a prospective study. Semin Arthritis Rheum. 2022;55:152018.
19. Sanada A, Abe N, Bohgaki M, et al. Therapeutic effectiveness of upadacitinib combined with glucocorticoid on remission induction and maintenance in giant cell arteritis. Rheumatology. 2022;61:e274-e6.
20. Prigent K, Aouba A, Aide N, et al. JAK inhibitor effectiveness in giant-cell arteritis with large-vessel involvement assessed by 18F-FDG PET-CT. Clin Nucl Med. 2022;47:234-5.
21. Eriksson P, Skoglund O, Hemgren C, et al. Clinical experience and safety of Janus kinase inhibitors in giant cell arteritis: a retrospective case series from Sweden. Front Immunol. 2023;14:1187584.
22. 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;81:861-7.
23. Tulunay A, Dozmorov MG, Ture-Ozdemir F, et al. Activation of the JAK/STAT pathway in Behcet's disease. Genes Immun. 2015;16:170-5.
24. Ortiz Fernández L, Coit P, Yilmaz V, et al. Genetic association of a gain-of-function IFNGR1 polymorphism and the intergenic region LNCAROD/DKK1 with Behçet's disease. Arthritis Rheumatol. 2021;73:1244-52.
25. Puccetti A, Fiore PF, Pelosi A, et al. Gene expression profiling in Behcet's disease indicates an autoimmune component in the pathogenesis of the disease and opens new avenues for targeted therapy. J Immunol Res. 2018:4246965.
26. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis. 2018;77:808-18.
27. Liu J, Hou Y, Sun L, et al. A pilot study of tofacitinib for refractory Behçet's syndrome. Ann Rheum Dis. 2020;79:1517-20.
28. Abdulahad WH, Lamprecht P, Kallenberg CG. T-helper cells as new players in ANCA-associated vasculitides. Arthritis Res Ther. 2011;13:236.
29. Marinaki S, Kälsch AI, Grimminger P, et al. Persistent T-cell activation and clinical correlations in patients with ANCA-associated systemic vasculitis. Nephrol Dial Transplant. 2006;21:1825-32.
30. Beketova TV, Volkov MY, Naryshkin EA, et al. Imatinib mesylate use in refractory eosinophilic granulomatosis with polyangiitis: a literature review and a case report. Clin Rheumatol. 2018;37:1729-35.
31. Liu Y, Ji Z, Yu W, et al. Tofacitinib for the treatment of antineutrophil cytoplasm antibody-associated vasculitis: a pilot study. Ann Rheum Dis. 2021;80:1631-3.

32. Rimar D, Alpert A, Starosvetsky E, et al. Tofacitinib for polyarteritis nodosa: a tailored therapy. Ann Rheum Dis. 2016;75:2214-6.

33. Zhu KJ, Yang PD, Xu Q. Tofacitinib treatment of refractory cutaneous leukocytoclastic vasculitis: a case report. Front Immunol. 2021;12:695768.

34. Roy D, Sathyanarayana VA, Nagaraju B, et al. Tofacitinib as monotherapy in cutaneous polyarteritis nodosa: a case series. Rheumatol Adv Pract. 2023;7:rkad049.

35. Singh JA. The Emerging safety profile of JAK inhibitors in rheumatic diseases. BioDrugs. 2023;37:625-35.

36. Asemota U, Greenberg S, Gulati A, et al. Tofacitinib-induced antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis with crescentic glomerulonephritis. Cureus. 2021;13:e18663.

37. Tığlıoğlu M, Tığlıoğlu P, Yıldız A, et al. Leukocytoclastic vasculitis due to ruxolitinib treatment: a rare adverse effect. J Clin Pharm Ther. 2022;47:544-7.

38. Itoh I, Kasuno K, Yamamoto C, et al. IgA Vasculitis Developed as an adverse effect of tofacitinib taken for rheumatoid arthritis. Intern Med. 2020;59:817-21.