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Prospects of targeting JAK/STAT signal transduction pathways for vasculitis

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Abstract. – Vasculitis is the inflammation of blood vessels caused by autoimmunity and/or autoinflammation, and its etiology and pathogenesis remain largely unknown. The Janus kinase (JAK) and Signal transduction Transcription Activator (STAT) signal transduction pathways are a group of molecules involved in the major pathways by which many cytokines exert and integrate their functions, and their dysregulation has been implicated in the pathogenesis of a variety of autoimmune diseases. However, current data supporting the role of the JAK/STAT pathway in the development of vasculitis is limited. In terms of treatment, glucocorticoids and immunosuppressants have been the standard therapy. However, because of the huge burden of treatment side effects, people have long waited for new treatment options. JAK inhibitors reduce the production of multiple cytokines and inhibit inflammation by targeting the JAK/STAT pathway, and have the advantage of rapidly acting in oral formulations, reducing glucocorticoid dependence and associated adverse events, especially in refractory cases. Therefore, JAK inhibitors are expected to be a promising drug for the treatment of vasculitis.

Key Words:
Giant cell arteritis, JAK inhibitors, JAK/STAT pathway.

Introduction

Vasculitis is a group of heterogeneous systemic inflammatory diseases characterized by inflammation of the vascular wall, resulting in intimal hyperplasia, outer membrane thickening, and intramural vascularization, damage to vascular integrity and tissue perfusion, and ultimately damage to various organs. According to the size of the vessels involved, vasculitis can be divided into large, medium, and small vessels[1].

The pathogenesis of vasculitis may be related to the imbalance of the Janus kinase (JAK) and Signal transduction Transcription Activator (STAT) pathway. Studies[2] have found that the JAK-STAT pathway has enhanced activity in the diseased vessels of patients with vasculitis. In addition, T cells are dominant in the transmural lesions of vasculitis, and the production of cytokines in T cells is dependent on the JAK-STAT pathway[3], indicating the importance of the JAK-STAT pathway in the pathogenesis of vasculitis.

The main treatments for vasculitis are glucocorticoids (GC) and immunosuppressants such as cyclophosphamide[4]. However, people have long been waiting for new treatment options due to the high side effects of treatment. Subsequently, new therapeutic drugs, such as rituximab that depletes B cells[5], receptor inhibitors that block complement 5a receptors[6], tocilizumab that block IL-6 receptors[7], and abatacept that block T cell co-stimulatory signals[8], can induce vascular remission and reduce the amount of GC and immunosuppressant. Although the above medications are effective and safe, many patients experience relapse after discontinuation. The accumulated side effects of GC due to multiple relapses are significant and, therefore, remain unmet clinical needs.

In recent years, there has been increasing interest in modulating the JAK-STAT pathway for the treatment of autoimmune diseases. JAK inhibitors have shown[9] good efficacy in improving the clinical signs and symptoms of these diseases. JAK inhibitors can target the JAK-STAT path-

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way, inhibit the overactivation of immune cells and reduce the level of inflammatory cytokines, and their safety has been proven[10] in other rheumatic diseases. More and more clinical trials[3,10] have been conducted for vasculitis. Therefore, JAK inhibitors are expected to be a promising drug for the treatment of vasculitis.

JAK-STAT Pathway

JAK is an intracellular non-receptor tyrosine kinase. At present, four types of JAK have been identified, named JAK-3 and Tyrosine kinase (TYK) 2, which are essential for signal transduction initiated by cell surface membrane receptors in mammals[11]. JAK is widely expressed in various tissues and cells, which is the basis for their widespread participation in various signal transduction pathways[12]. They are cytoplasmic tyrosine kinases that phosphorylate tyrosine residues on themselves (autophosphorylation) or adjacent molecules (transphosphorylation), including STAT. The latter is a family of transcription factors located downstream of JAK and composed of STAT1-4, STAT5A, STAT5B, and STAT6[13]. Studies[14] have found that both CD4 + and CD8 + cells in the peripheral blood of patients with vasculitis showed increased expressions of JAK and STAT, indicating increased activity of this pathway. Protein kinases are important modulators of cell function and achieve intracellular signal transduction through the linkage between JAK, TYK2 isomers and STAT members. The activity of each JAK depends on the selective interaction with the cytokine receptor. Each cytokine receptor provides a specific combination with the JAK kinase and is closely associated with targeted therapy. However, because different cytokines may share a JAK molecule, blocking it may be associated with some adverse reactions[15].

Distribution and Expression of JAK and STAT in Blood Vessels

The JAK/STAT signaling pathway is responsible for regulating cell homeostasis; therefore, overactivation of this signaling axis may lead to autoimmune diseases[16], as well as vascular damage. *In vitro*, the expression of p-JAK1, p-JAK2, p-JAK3 and p-STAT3 in endothelial cells was increased after co-culture of IL-17 with human umbilical vein endothelial cells[17]. Collagen-induced arthritis rats, especially if given a high-fat diet, develop inflammatory infiltration of the aorta and can, therefore, be used as a model for greater vasculitis. By biopsies of rat aorta, we found that p-STAT3 expression levels were significantly increased in vascular endothelium and mesolayer, indicating the potential role of JAK/STAT activation in vascular inflammation[17]. Recent studies[3,17] have quantified transcripts of STAT1-4, STAT5a and STAT6 in temporal artery biopsy samples from patients with vasculitis and non-inflammation. Transcripts of all members of the STAT family were found[3] to be low in abundance in normal arteries, and STAT3, STAT5a, and STAT6 remained poorly expressed in arteries affected by vasculitis. In contrast, STAT1, STAT2, and STAT4 transcripts are abundant in vasculitis arteries. In a recent study[18], the expression of STAT1 and STAT2 in aortic tissues was significantly up-regulated in patients with vasculitis compared with controls. In general, all STATs tended to be up-regulated except STAT5A (no difference) and STAT5B (down-regulated expression). In addition, when interstitial lung diseases caused by other causes may involve pulmonary vessels, resulting in vasculitis, JAK2 can be distributed in the intima and media of pulmonary arterioles of patients, and the expression of p-JAK2 in the pulmonary artery is enhanced[19]. STAT3 is present in the intima and media of the patient's pulmonary arteriole[20].

Pathogenesis of JAK-STAT Pathway in Vasculitis

JAK/STAT pathway activation is closely associated with the production of multiple cytokines, including type I and type II cytokines, and is, therefore, involved in the pathogenesis of vasculitis (Figure 1). The JAK/STAT pathway is an evolutionarily conserved pathway that mediates the action of many different molecules, including type I cytokines: Interleukin (IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-12, IL-13, IL-15, IL-21, IL-23), granulocyte-macrophage colony-stimulating factor (GM-CSF), etc.[21]. Type II cytokines include type I (IFN-α/β), type II (IFN-γ) interferon (IFN) and IL-10-related cytokines (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26)[21] and the tumor necrosis factor (TNF) family (TNF-α). In vasculitis, the levels of cytokines such as IL-1, IL-4, IL-6, IL-8, IL-9, IL-10, IL-12, IL-17, IL-21, IL-23, IFN-γ, type I IFN, TNF-α and GM-CSF are increased[22]. Elevat-

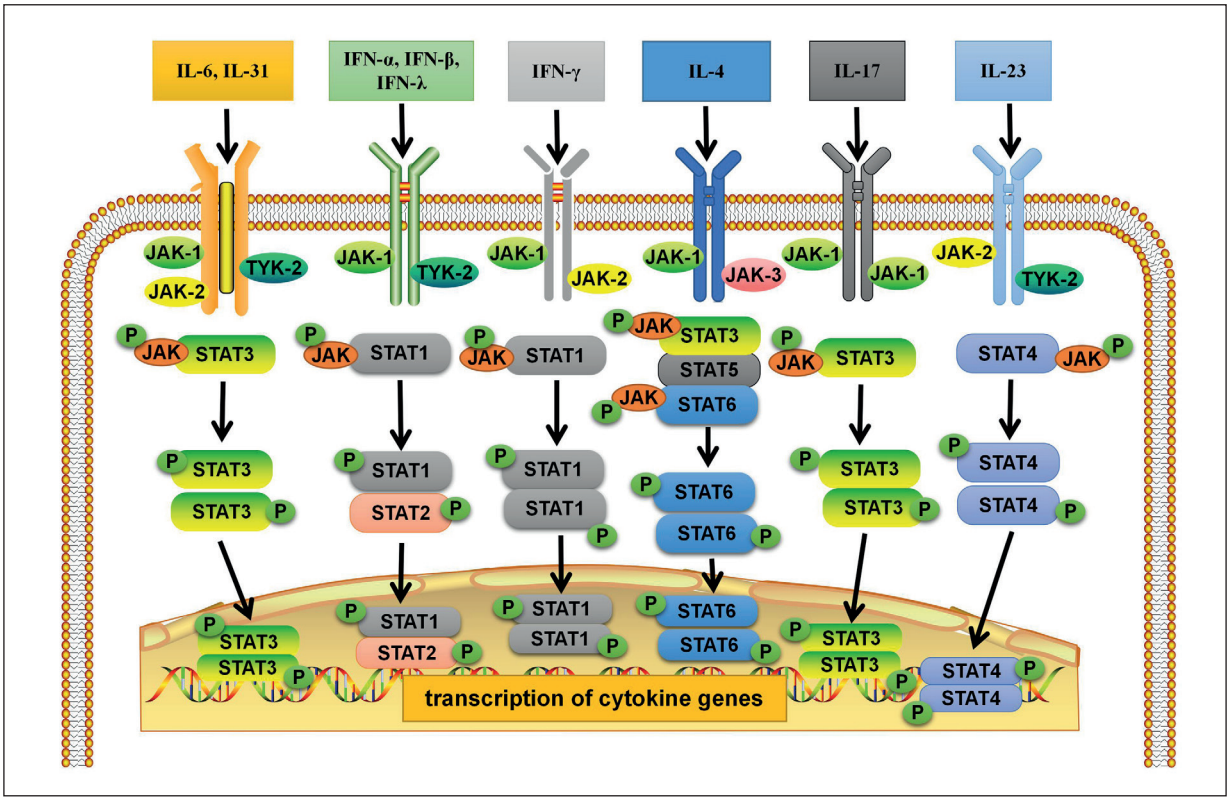

Figure 1. The JAK-STAT pathway activates immune cells at the subcellular level in vasculitis.In vasculitis, levels of various cytokines are elevated, and these ligands bind to receptors on the surface of immune cells, such as T cells, to induce dimerization of JAK. The receptor-associated JAK is then activated and phosphorylates the tyrosine residue in the tail of its receptor to form p-JAK. Subsequently, these phosphorylation sites act as docking sites for STAT and bind to them via its SH2 domain, causing tyrosine phosphorylation and activation of STAT to form p-STAT. Most STAT forms a homodimer; However, heterodimers such as STAT1/2 are also present. As a result, STAT forms dimers and is transferred from the cytoplasm to the nucleus, where they act as transcription factors regulating gene expression. IL, Interleukin; IFN, interferon; P, phosphate; JAK, janus tyrosine kinase; STAT, signal transducers and activators of transcription.

ed cytokines activate the JAK/STAT pathway after binding to corresponding receptors on the immune cell surface, regulating the immune response at the subcellular level (Figure 1). When activated, immune cells (such as macrophages and T cells) can secrete a variety of cytokines, which can induce T cells to differentiate into different T cell subtypes and infiltrate the vascular wall, eventually leading to vasculitis (Figure 2) while activating themselves with positive feedback. In the vascular wall of patients with vasculitis, infiltrated T cells include T-helper (Th) cells 1 and Th17, etc.[1,2].

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In vasculitis, when immune cells are activated, they can secrete a variety of cytokines. Under the action of different cytokines, initial T cells can differentiate into Th1, Th17, TFH and TRM cells. While secreting a variety of cytokines to activate immune cells in a positive way, these T cells infiltrate the vascular wall, resulting in intima hyperplasia, outer membrane thickening and intramural vascularization. Vascular wall thickening can lead to narrowing of the vascular cavity, tissue blood perfusion insufficiency, and eventually damage to various organs.

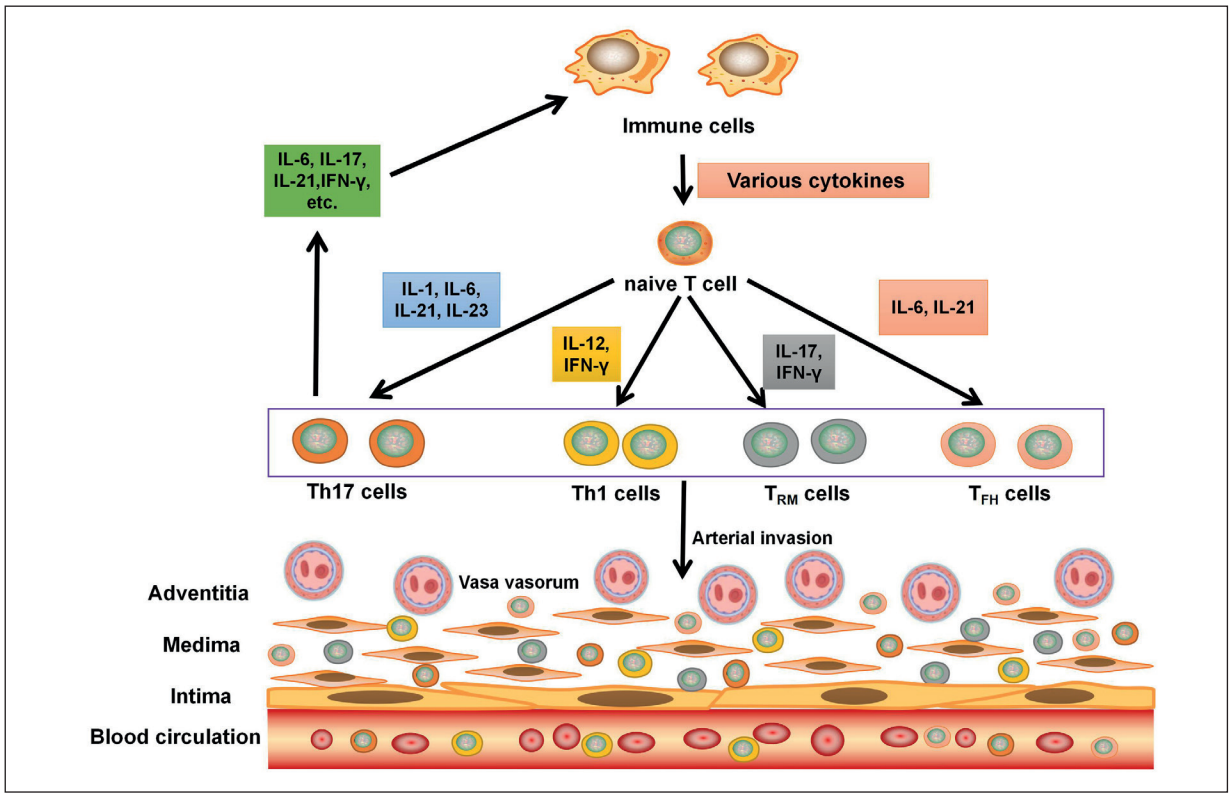

Figure 2. Activation of the JAK-STAT pathway in vasculitis leads to T cell imbalance. In vasculitis, when immune cells are activated, they can secrete a variety of cytokines. Under the action of different cytokines, initial T cells can differentiate into Th1, Th17, TFH and TRM cells. While secreting a variety of cytokines to activate immune cells in a positive way, these T cells infiltrate the vascular wall, resulting in intima hyperplasia, outer membrane thickening and intramural vascularization. Vascular wall thickening can lead to narrowing of the vascular cavity, tissue blood perfusion insufficiency, and eventually damage to various organs. IL, Interleukin; IFN-γ, interferon-γ; Th, T helper; TRM, tissue-resident memory T; TFH, follicular helper T.

Application of JAK Inhibitors in Vasculitis

Tofacitinib

Tofacitinib is a small molecule oral selective inhibitor of JAK1/JAK3 and, to a lesser extent, JAK2 and tyrosine kinase 2 (TYK2). It is clinically suitable for the treatment of rheumatoid arthritis (RA) and ulcerative colitis, and its efficacy and safety have been extensively evaluated in a series of phase 1-3 clinical trials[23-25]. Previous studies[2] have found that tofacitinib can reduce the proliferation rate of diseased T cells and the production of IFN-γ, IL-17 and IL-21 in vasculitis, as well as the number of microangiogenesis, intimal hyperplasia and CD4+CD103+ tissue-resident memory T cells.

In terms of vasculitis, the first observational study[26] of a JAK inhibitor in the treatment of TAK compared tofacitinib (n=27) with methotrexate (n=26) for induction of remission. Tofacitinib (5 mg twice daily) had a higher rate of complete response at 6 and 12 months (23/27, 85% *vs.* 16/26, 61%, p=0.07; 23/26, 88% *vs.* 13/23, 56%, p=0.02), the median time without recurrence was longer, but the recurrence rate and imaging improvement rate did not reach statistical significance. During the 12-month treatment period, only 1 patient (3.70%) in the tofacitinib group developed herpes zoster[26]. In addition, in a recent study[14], tofacitinib treatment of TAK resulted in a decrease in Th1 and Th17 cells and an increase in regulatory T cells (Tregs)/effector T cells, confirming a decrease in CD4+ effector T cell activation/differentiation *in vivo*. The authors[14] also demonstrated that the expression of pSTAT5A in CD4 +T cells was immediately reduced after tofacitinib administration.

Tofacitinib is also used for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV). Studies[27] have shown that 10

patients with AAV treated with 5 mg twice daily achieved complete response in 9 patients and partial response in 1 patient. No patient relapsed during follow-up. Eye involvement (scleritis, blurred vision, eyeball swelling) in 5 patients with granulomatous polyvasculitis (GPA) disappeared rapidly after treatment[27]. For eosinophil GPA patients, skin ulcers healed rapidly, and eosinophil returned to normal levels after 1 month of tofacitinib administration. Significant improvements in C-reactive protein (CRP) and ESR levels were observed in the third month[27]. At the same time, the dose of GC was reduced. However, there were 2 cases with adverse events, one patient with mild upper respiratory tract infection symptoms and the other patient with low-grade fever and fatigue[27]. In a patient with refractory polyarteritis nodosa, tofacitinib 10 mg twice daily was administered, and the patient's CRP, albumin, and white blood cell counts quickly returned to normal, symptoms were relieved, and prednisone treatment was reduced from 60 mg to 10 mg per day[28]. Re-evaluation of the response of the JAK-STAT pathway to IL-6 stimulation after treatment confirmed a weakened T cell response, similar to that of the healthy control group[28]. In addition, several case reports[29,30] have demonstrated the effectiveness of tofacitinib in other vasculitis, such as cutaneous leukocyte broken vasculitis and vascular Behçet's disease. These findings suggest that tofacitinib may be a promising new alternative therapy with efficacy and safety, especially for patients with refractory vasculitis.

Baricitinib

Baricitinib, an oral inhibitor of JAK1/JAK2, has shown[31-33] initial safety and efficacy in chronic immune-mediated inflammatory diseases such as RA and psoriasis. Due to its inhibitory effect on the Th17 (IL-6, IL-23) and Th1 (IL-12, IFN-γ) pathways[34], this small molecule is particularly suitable as a potential novel therapeutic agent for vasculitis.

Régent et al[35] reported a TAK patient with only temporary and incomplete clinical improvement after treatment with GC, methotrexate, tocilizumab, and infliximab. Superior mesenteric artery stenosis and inferior mesenteric artery stenosis were found on CTA, indicating treatment failure and moderate improvement of the patient's symptoms after the introduction of cyclophosphamide[35]. After the addition of baricitinib 4 mg/d treatment, the patient's symptoms and imaging were significantly improved, and the use of GC was reduced[35]. It suggests that JAK inhibitors may be an effective alternative for refractory vasculitis. In a recent study[36], 15 patients with recurrent giant cell arteritis (GCA) were enrolled and 14 completed all 52 weeks of baricitinib (4 mg/day). Thirteen patients were able to follow accelerated GC reduction, stop GC, and maintain disease remission, fully controlling subsequent recurrence, and only one (7%) relapsed during the study period. Fourteen patients had at least one adverse event, and the most common events included infection that did not require antibiotics (n=8), infection that required antibiotics (n=5), nausea (n=6), leg swelling (n=2), fatigue (n=2), diarrhea (n=1), abdominal pain (n=1), and symptomatic shingles in one patient[36]. This single-center, open-label study[36] provides preliminary evidence for the efficacy and safety of baricitinib. There are currently few studies on baricitinib in the treatment of vasculitis, and larger, double-blind, placebo-controlled studies are needed to further evaluate its efficacy and safety in patients with vasculitis.

Ruxolitinib

Ruxolitinib is a JAK1 and JAK2 inhibitor with moderate activity against TYK2 and has been used in psoriasis[37]. In vasculitis, when ruxolitinib was co-cultured with B cells and T follicular helper (Tfh) cells of TAK patients, it could further inhibit the maturation of B cells by inhibiting Tfh cells and also inhibit the secretion of IL-6[38]. However, when B cells and Tfh cells were respectively treated with ruxolitinib, there was no effect on the maturation of B cells[38]. In a recent study[14], the authors treated 3 cases of TAK with ruxolitinib. After treatment, CD25 expression of CD4+ T cells was decreased, the percentage of Treg cells was increased, Th1 and Th17 cells were decreased, and Tregs/Teffs ratio was increased, which confirmed the decreased activation/differentiation of CD4+ effector T cells *in vivo*. The expression of pSTAT 5A in CD4 +T cells was immediately reduced[14]. Rusotinib also effectively reduced systemic inflammation, reduced CRP levels in 2 TAK patients, and allowed two-thirds of patients to reduce their GC dose[14]. It suggests that rusotinib may be a promising treatment for vasculitis.

Upadacitinib

Upadacitinib is a selective JAK1 inhibitor, which is 74 and 58 times more selective than

Table I. Progress in clinical trials of JAK inhibitors.

Disease	Study identifier	Study type	Number of patients	Intervention	Study duration	Primary outcome measures	Secondary outcome measures
GCA	NCT03725202	Phase 3 Double blind Controlled Multicenter	420	Upadacitinib/ corticosteroid; Placebo	52 weeks	Sustained remission	Sustained complete remission, cumulative exposure to corticosteroid(s), disease flare, SF-36, FACIT-F, TSQM, adverse events
TAK	NCT04299971	Phase 4. Randomized but open-label.	130	Tofacitinib/ methotrexate	24 weeks	Disease remission is evaluated	Disease remission at 48 weeks. Prednisone dose reduction at endpoint. disease relapse in the follow-up. Vascular progression in angiographic examination at 6 months and 12 months. Change of the quality of life with questionnaire SF-36, MOS-sleep scale and the Fatigue severity scale.
TAK	NCT04161898	A Phase 3, Multicenter, Randomized, Double-Blind	56	Upadacitinib/ corticosteroid; Placebo	52 months	Time to first relapse of TAK from baseline.	Time to first relapse of TAK by Kerr Criteria from baseline and worsening of imaging assessment due to TAK from baseline.

GCA, giant cell arteritis; TAK, Takayasu arteritis; SF-36,36-Item Short Form Health Survey; FACIT-F, Functional Assessment of Chronic Illness Therapy -Fatigue; TSQM,Treatment Satisfaction Questionnaire for Medication; MOS, Medical Outcomes Study.

JAK2 and JAK3 *in vitro*[39], and has the ability to inhibit IL-6, IL-17, and IFN axes. Clinical studies[40,41] have demonstrated its efficacy in treating PsA and RA. Sanada et al[42] reported a case of GCA accompanied by prostate-specific antigen (PsA). Laboratory results showed elevated Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). On imaging, Doppler ultrasound showed a halo sign around the vascular lumen, MRI showed bilateral vertebral artery wall thickening, and PET showed high fluorodeoxyglucose uptake in systemic arteries, including the aorta. Temporal artery biopsy showed highly narrowed blood vessels with fragmented internal elastic plates and invasion of the media by inflammatory cells, including lymphocytes, histopathocytes, and multinucleated giant cells. After treatment with upadacitinib and GC, the patient's symptoms, laboratory examination, imaging, and pathology were all improved[42], which also suggested the efficacy of upadatinib combined with GC in inducing and maintaining GCA. Another phase 3 multicenter, randomized controlled study is underway to evaluate the safety and efficacy of upadacitinib in patients with GCA. Although the efficacy of selective JAK1 in inhibiting vascularization needs to be determined in clinical trials, this case suggests that upadacitinib may be a promising agent for the induction and maintenance of vasculitis.

JAK Inhibitors in Clinical Trials in Vasculitis

At present, there is little real-world data on the efficacy of JAK inhibitors in the treatment of vasculitis, which is mainly focused on case reports. The safety and effectiveness of JAK inhibitors need to be confirmed by large-scale prospective studies. Despite very limited data, the potential benefits of JAK inhibitors for vasculitis could have a significant impact on patient management, especially in the context of treatment resistance[43]. Current ongoing clinical studies on JAK inhibitors are shown in Table I.

Conclusions

The JAK-STAT pathway is a highly conserved signal transduction pathway that plays a role in various physiological processes. Over the past decade, the newly discovered link between the JAK-STAT pathway and human autoimmune diseases has provided important insights into the pathogenesis of vasculitis mediated by this pathway. JAK inhibitors have shown[44] good efficacy in other autoimmune diseases (such as RA and PsA), and the evidence for their safety is accumulating. The clinical indications for JAK inhibition may be further expanded to include the treatment of vasculitis. There is currently little data to support the use of JAK inhibitors in clinical practice in vasculitis. However, some published case reports and studies in the literature may indicate the consideration of this approach in very severe and refractory vasculitis. Therefore, this drug class has the potential to effectively treat many difficult-to-control diseases, but further assurance of continued clinical studies of JAK inhibitors is needed to determine the long-term safety of the use of this drug.

Ethics Approval
Not applicable.

Informed Consent
Not applicable.

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Conflict of Interest
The authors have declared no competing interests.

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