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REVIEW ARTICLE

Targeting cytokines and potentiality of JAK–STAT inhibition in systemic sclerosis

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Abstract

Systemic sclerosis (SSc) or scleroderma is an autoimmune disease of unknown etiology, the treatment of which has garnered increased research interest. Associated symptoms range from localized or diffused skin tightening to multiple organ failure, including the lungs, kidneys, heart, and gastrointestinal tract, with considerable morbidity and mortality. Given that several cytokines contribute to the immune pathogenesis of SSc, efforts have been made toward the development of treatments targeting these cytokines to control disease progression. Indeed, anti-cytokine therapy has emerged as a new therapeutic intervention. Recently, the Janus kinase signal transducer and activator of transcription (JAK–STAT) pathway has been investigated as a novel candidate for the fibrogenic pathology of SSc. However, a comprehensive scientific review of the targeted therapy for SSc has been hampered by the rarity and heterogeneous nature of the disease. In this review, we provide an overview of cytokines involved in the innate and adaptive immune pathogenesis of SSc based on recent scientific data. In particular, we focus on targeted anti-cytokine therapy and the emerging role of the JAK–STAT inhibitor, a prospective therapeutic agent for the reversal of disease pathogenesis.

KEYWORDS
cytokine, fibrosis, JAK–STAT inhibitors, scleroderma, systemic sclerosis

1 | INTRODUCTION

Systemic sclerosis (SSc) or scleroderma is a rare heterogeneous disease characterized by tripartite pathogenesis—microvascular injury, immune cell activation, and chronic inflammation—leading to fibrosis of the skin and viscera.[1,2] However, the precise pathogenic mechanism underlying this disease remains unknown with no targeted therapy having been approved for the reversal of fibrosis in SSc.

Cytokines are essential regulators of immune reactions in paracrine, autocrine, or endocrine signaling and play a major role in the immune pathogenesis of SSc.[3] Moreover, they serve to bridge the innate and adaptive immune responses, which is critical in disease pathogenesis. Studies over the past few decades have demonstrated that targeting fibrogenic cytokines or cytokine receptors by blocking their signaling pathways is an effective strategy in the treatment of SSc. In particular, the JAK–STAT signaling pathway is reportedly

involved in cytokine-driven autoimmune disorders, and its inhibitors have been studied to understand its potential mechanism in the fibrogenesis of SSc.[4]

Here, we highlight the recent advances made in the understanding of cytokine-related immune pathogenesis of SSc, key cytokines, and their targeted therapies as well as the role of JAKs inhibitors as a new avenue for potential cytokine-targeted therapy for patients with SSc.

2 | CYTOKINE IMMUNOPATHOGENESIS OF SSC

The innate immune system serves as the first line of defense against pathogens and environmental damage, without mounting a memory response. Innate immune cells, such as neutrophils, macrophages, and dendritic cells, present antigens to T cells after recognition of pathogen-associated molecular patterns, damage-associated molecular patterns (DAMPs), and microbe-associated molecular patterns via pattern recognition receptors like toll-like receptors (TLRs).[5,6] Proinflammatory and fibrogenic cytokines have been detected in the innate arm during the early and late stages of SSc.[6–8]

TLRs are transmembrane proteins that recognize microbial antigens released by dying cells, and trigger cytokine secretion and inflammation upon activation. Innate immune signaling triggered by DAMPs via TLRs was recently described as a potential key driver of persistent fibrosis in SSc.[3,5,6,9] More specifically, injection of anti-TLR2-specific antibodies (Ab) reduces interleukin (IL)-6 levels in fibroblasts of patients with SSc,[10,11] while an endosomal TLR3 ligand in monocytes has been shown to activate fibrogenesis in SSc.[12] Upregulation of TLR3 activation in SSc dermal fibroblasts results in the increased production of IL-6 and monocyte chemoattractant protein (MCP)-1, leading to the recruitment of tissue monocytes.[13] Stimulation of TLR4 ligands enhances transforming growth factor (TGF)-β signaling that induces fibrosis in SSc.[14] TLR4-deficient mice with BLM-induced fibrosis showed reduced IL-6 levels, B-cell activation, and inflammatory cell infiltration.[15] Meanwhile, Epstein–Barr virus (EBV) genes have been detected in SSc skin biopsies, and EBV-infected SSc fibroblasts have been shown to induce TLR7 and TLR9 mRNA expression via induction of interferon (IFN)-stimulated genes and TGF-β-regulated genes.[16]

Mononuclear cells, such as circulating monocytes and tissue macrophages, secrete profibrotic cytokines, including TGF-β, IL-6, MCP-1, platelet-derived growth factor (PDGF), endothelin, and connective tissue growth factor (CTGF), and are implicated in SSc pathogenesis.[17] Proinflammatory T-helper (Th)1-derived M1 or profibrotic Th2-derived M2 macrophages produce TGF-β and other fibrogenic cytokines and enhance fibrogenesis.[5,18,19] Thus, soluble $CD163^+$ M2 macrophage levels are increased in patients with SSc compared to healthy controls.[20] However, treatment with pan-JAK inhibitors (tofacitinib and ruxolitinib) suppresses M1 and M2 markers and prevents skin and lung fibrosis in the hypochlorous acid (HOCL)- and bleomycin (BLM)-induced SSc models.[21,22] Moreover, nintedanib reduces the number of M2 macrophages and alleviates fibrosis in a Fra2 mouse model of SSc.[23]

Plasmacytoid dendritic cells (pDCs) produce large amounts of type I IFN via TLR7 and 9 antigen recognition.[24,25] Although pDCs have been detected in the skin of patients with SSc and mice after BLM treatment,[25,26] their depletion in a murine model of SSc attenuates skin and lung fibrosis.[26] pDCs are also reduced by pan-JAK inhibitor administration in BLM-induced SSc mice.[21] Moreover, mast cells are a major source of TGF-β, contain vesicles of various cytokines and proinflammatory molecules, and are correlated with the degree of SSc skin fibrosis.[6,27] Thus, innate immune cells and their cytokines may be implicated at the onset, and during the disease progression, of SSc, while targeting cytokines in the innate arm of the immune system represents a potential therapeutic strategy.

The adaptive immune response involves antigen-driven activation of T cells that lead to the secretion of proinflammatory cytokines, which in the case of the fibrotic cascade leads to excessive collagen synthesis.[3,28,29] In patients with SSc, the CD4+ and CD8+ T cells that produce Th2 cytokines (IL-4 and IL-13), and Th17 cells that produce IL-17, are increased, thereby promoting collagen synthesis.[3,5,30,31] In contrast, the Th1 cytokine IFN-γ regulates collagen degradation by controlling the balance of matrix metalloprotein (MMP) and tissue inhibitors of metalloproteinases (TIMP). IFN-γ also downregulates TGF-β and represses the Th2 response.[31,32] Thus, in SSc, T-cell polarization skewing toward the Th2 phenotype promotes matrix deposition via secretion of-IL-4, IL-5, IL-6, IL-13, and MCP-1.[31] Additionally, dysregulation of regulatory T cells (Treg) has been detected, however, its role in SSc remains controversial.[30] Therefore, cytokine-producing T cells are important drivers of autoimmunity and inflammation in patients with SSc and are critical targets in controlling disease pathogenesis.

B cells play a critical role in SSc pathogenesis by producing fibrogenic cytokines, such as IL-6, TGF-β, and autoantibodies.[33,34] B cells, following activation by T-cell-driven cytokines, can act as antigen-presenting cells, release cytokines, aid T-cell differentiation and dendritic cell proliferation, or directly stimulate fibrosis.[17] Moreover, CD19 is also upregulated in patients with SSc, and its depletion eliminates SSc-specific autoantibodies with reduced IL-6 production from B cells.[3,5,35,36] Regulatory B (Breg) cells—a small subset of B cells—exert regulatory functions in autoimmunity and produce IL-10.[37] A previous study reported that B-cell-activating factor (BAFF) levels are elevated in the sera of patients with SSc, while BAFF inhibition serves to maintain the balance between effector B (Beff) and Breg cells via IL-6 and IL-10 regulation.[38] Furthermore, in a murine model of SSc, sclerodermatous chronic graft-versus-host disease (Scl-cGVHD), the absence of regulatory B cells induces disease onset, and in patients with SSc, reduced abundance of Breg cells correlates with interstitial lung disease (ILD) progression.[39,40] Therefore, IL-10-producing regulatory B cells may play an inhibitory role in SSc pathogenesis, and selective B-cell depletion, thus, B-cell-targeted anti-cytokine therapy represents a promising SSc treatment option.

3 | KEY CYTOKINES AND THEIR ANTAGONISTS

3.1 | TGF-β and CTGF

TGF-β is an essential cytokine that is triggered in SSc fibrogenesis, and induces epithelial, endothelial, and mesenchymal cells to develop a profibrotic phenotype.[2] Moreover, TGF-β produces collagen and stimulates CTGF, which is a downstream mediator. In fact, serial injection of TGF-β and CTGF induces skin fibrosis, during which TGF-β transiently causes subcutaneous fibrosis, and subsequent injection of CTGF promotes persistent fibrosis.[32,36] Indeed, elevated levels of TGF-β and CTGF have been observed in patients with SSc and in SSc mouse models.[2,3] Among the three isoforms of TGF-β, TGF-β1 is most strongly involved in fibrosis, however, inhibition of all active TGF-β isoforms may be necessary to effectively treat and prevent fibrosis.[36,41] Fresolimumab, a humanized anti-TGF-β Ab, blocks TGF-β signaling by binding to all three TGF-β isoforms and reduces skin biomarkers of fibrosis.[42,43] However, a recombinant human antibody (CAT-192) against active TGF-β1 proved to be a treatment option for early-stage diffuse cutaneous SSc in phase I/II clinical trials.[36] Meanwhile, abituzumab, which targets the αVβ6 integrin/TGF-β pathway, is currently being investigated in phase II randomized controlled trial for ILD in patients with SSc.[4,43] Moreover, iloprost—a prostacyclin analog—reduces the level of CTGF in the skin of patients with SSc.[44] Furthermore, the anti-CTGF antibody pamrevlumab (FG-3019) reduces inflammation, skin fibrosis, and vasculopathy, while attenuating dermal fibrosis in mice models of SSc.[45] Therefore, blocking the TGF-β-CTGF pathway represents a potential anti-cytokine treatment for SSc.

3.2 | PDGF and VEGF

PDGF is a potent proinflammatory cytokine produced by platelets, macrophages, endothelial cells, and fibroblasts, and has a pathogenic role in dermal fibrosis as well as endothelial injury.[3,46] PDGF promotes extracellular matrix (ECM) synthesis, secretion of the profibrotic cytokines IL-6 and MCP-1, and reactive oxygen species generation in fibroblasts.[2,3] Meanwhile, vascular endothelial growth factor (VEGF) is a potent proangiogenic cytokine involved in SSc pathogenesis.[47] Its overexpression is implicated in the exacerbation of vasculopathy and skin fibrosis in the early inflammatory phase of SSc.[43] Indeed, serum VEGF levels are significantly elevated in patients with SSc and are associated with disease duration, systolic pulmonary artery pressure, skin fibrosis, nail fold capillary density, and systemic organ involvement.[48] Nintedanib—a tyrosine kinase inhibitor that acts on PDGF, VEGF, and VEGF receptors—reduces cytokine-induced fibrosis and is the first FDA-approved agent for the treatment of ILD in patients with SSc.[4,5] Similarly, imatinib interferes with the fibrotic process by selectively inhibiting both TGF-β and PDGF signaling pathways in vivo and in vitro.[3] Hence, anti-PDGF or VEGF agents represent potentially effective therapeutic targets for SSc.

3.3 | IL-6

IL-6 is a pleiotropic cytokine produced by monocytes, activated B cells, fibroblasts, and endothelial cells; IL-6 is profibrotic through gp130 protein signaling.[2,17] Through the STAT3-dependent pathway, IL-6 enhances canonical TGF-β signaling via Smad3 activation and increases TIMP synthesis, resulting in collagen accumulation and increased myofibroblast differentiation.[49] Recently, studies have reported the amelioration of skin and lung fibrosis in SSc mice models via the reduction of IL-6 levels.[21,38] High levels of IL-6 expression have been observed in cultured fibroblasts from patients with SSc and are implicated in sclerosis and autoimmunity in mouse models of SSc.[38,50] Serum IL-6 levels are significantly linked to targeting organ fibrosis and disease progression, while high levels of the IL-6 receptor (IL-6R) and anti-IL-6 autoantibodies have been found in patients with SSc.[2,36,49] A humanized anti-IL-6R antibody, tocilizumab, improves early SSc-associated lung disease.[51,52] Therefore, targeting IL-6 is a potential therapeutic strategy for the reversal of fibrogenesis in SSc.

3.4 | IL-10

IL-10 is a well-known, anti-inflammatory cytokine that performs a regulatory function by inhibiting proinflammatory cytokines in autoimmune diseases; in contrast, it may enhance the immune response in SSc pathogenesis.[50,53] BAFF has been shown to increase IL-6-producing Beffs and attenuate IL-10-producing Bregs. Consequently, the inhibition of BAFF attenuates skin and lung fibrosis in BLM-induced SSc by regulating these cytokines.[38] Additionally, IL-10-producing Bregs suppress skin fibrosis in the Scl-cGVHD model.[39] Reduction in IL-10-producing B cells may accelerate autoantibody production as the level of Breg cells is inversely correlated with SSc disease activity.[40] A recent study showed that vitamin D induces IL-10 secretion from Tregs in patients with SSc and suppresses the immune response.[54] Moreover, B-cell production of IL-10 is impaired in the spleen of the HOCL-induced fibrosis mouse model during the early inflammatory stage, as opposed to that in the control group.[55] Additionally, serum levels of IL-10 strongly indicate the extent of skin thickening in patients with SSc[50]; hence, the role of IL-10 in disease pathogenesis has become an area of interest in SSc, however, it remains unclear whether elevated IL-10 contributes to disease recovery or represents a compensatory physiological response.

3.5 | IL-4 and IL-13

IL-4 and IL-13 are related cytokines that have functional redundancy and regulate type II immune responses in SSc pathogenesis.

Both cytokines induce fibrosis in TGF-β-dependent and TGF-β-independent manners[56] and participate in the interplay between innate and adaptive immune cells. As such, they contribute to the transition from the early inflammatory to late fibrotic phase of SSc. T cells induce collagen and ECM production via fibroblasts through IL-4, IL-13, and TGF-β.[31,56] Moreover, type 2T-helper (Th2) cell lineages that produce IL-4 or IL-13 predominate over Th1 cell polarization, which produces IL-2 or IFN-γ during the SSc fibrotic process.[17,31] Serum levels of IL-4 and IL-13 are higher in patients with SSc than in healthy controls.[3] Recently, a study showed that imatinib effectively reduces IL-4-producing T cells and exerts therapeutic effects on T-cell subsets in the bronchoalveolar lavage of patients with SSc.[56] Similarly, romilkimab (SAR156597)—a monoclonal antibody bispecific for IL-4 and IL-13—is currently being tested in phase II clinical trial of SSc and has demonstrated a significant reduction in skin fibrosis.[4,57] Accordingly, targeting the Th2 cytokines, IL-4 and IL-13, is a promising anti-cytokine therapy for SSc.

3.6 | IL-17A

Among the six members of the IL-17 cytokine family (IL-17A–F), IL-17A is the pioneer cytokine mostly studied in Th17 immunopathogenesis of SSc.[58,59] Th17 cells predominantly secrete IL-17A and IL-17F, but their response is skewed toward the IL-17A pathway than the IL-17F pathway.[59] Nakashima et al. first observed no increase in IL-17F levels in the sera of patients with SSc. However, a proportional increase in the IL-17F population with disease duration and severity has also been reported.[60] High counts of IL-17E$^+$ and low counts of IL-17C$^+$ cells have been reported in the dermis of patients with SSc and morphea.[61,62] Although serum levels of IL-17A are elevated, and IL-17A mRNA expression is upregulated in the peripheral blood and lesional skin of patients with SSc,[63] its role remains controversial in disease pathogenesis. Some contradictory studies indicating no difference or lower level of IL-17A in the sera of patients with SSc exist.[59] However, it is thought to be involved in the production of profibrotic or proinflammatory cytokines and to enhance fibroblast proliferation. Moreover, its elevation is associated with disease onset and activity, modified Rodnan skin score, lung severity, telangiectasia, and pitting scars.[64] IL-17A induces IL-1, IL-6, IL-8, and tumor necrosis factor (TNF)α expression and endothelial cell adhesion molecules during fibrogenesis. In fact, Th17 cells—that primarily produce IL17A—are a major source of TGF-β and are increased in the dermis of patients with SSc.[65] IL-17A expression is also increased in BLM-induced SSc, TSK/+ mice, while Scl-cGVHG and IL-17A knockout mice exhibit amelioration of skin fibrosis in two animal models (BLM induced and TSK/+).[64] However, ECM turnover is enhanced by IL-17A according to the reduced ratio of Col1A2-to-MMP-1 mRNA levels. Brodalumab, a human anti-IL17R monoclonal antibody that binds to human IL-17RA and blocks biological activities of IL-17A and F, is currently in phase I and III clinical trials and shows positive outcomes. Other anti-IL-17 drugs, such as ixekizumab and secukinumab, are also being studied for SSc treatment.[59] Given that IL-17A signaling inhibits fibrogenic processes via the downregulation of CTGF and collagen synthesis,[36,66] it may represent an attractive target in SSC treatment.

4 | JAK INHIBITION IS A POTENTIAL THERAPEUTIC STRATEGY

JAKs are receptor-associated tyrosine kinases that include JAK1, JAK2, JAK3, and Tyk2. The binding of cytokines to their receptors recruits JAKs, which, upon activation, phosphorylate STAT proteins (STAT1–5A, 5B, and 6) that enter the nucleus and modulate cytokine gene expression.[67–69] Signaling via different JAKs and specific STATs is used by various type I and II cytokines for their respective gene expression and eliciting specific immune responses, as listed in Table 1. JAK–STAT signaling contributes to the cytokine pathogenesis of the innate and adaptive immune responses, ultimately leading to fibrogenesis in SSc (Figure 1). Key cytokines involved in SSc utilize JAK–STAT signaling to elicit their downstream immunological effects (Table 2) and thus, targeting multiple JAKs will inhibit major cytokine signaling pathways associated with SSc, effectively reversing fibrogenesis.

In human and mouse studies of SSc, JAK inhibitors have shown remarkable therapeutic efficacy and positive outcomes through the modulation of cytokine and cytokine receptors. Currently, a dearth of data has been provided regarding the efficacy of JAK inhibitors in SSc. Nevertheless, first- and second-generation JAK inhibitors capable of selectively and non-selectively block JAKs are currently under investigation in human and murine studies of SSc (Table 3). In a recent case report, tofacitinib was reported to cause clinical and histopathological regression of localized morphea.[70] More specifically, tofacitinib prevents bleomycin-induced SSc by affecting JAK–STAT3 signaling.[71] Tofacitinib diminishes skin and lung fibrosis in BLM-induced SSc by inhibiting proinflammatory cytokine production from T and B cells and promoting regulatory balance.[21] In a murine BLM-induced SSc model, tofacitinib

TABLE 1 Utilization of different JAKs and STATs by cytokines.[67,68,77,78]

JAK	STAT	Type I and type II cytokines involved in JAK–STAT signaling
JAK1	STAT1–3, 5, 6	IL-2, IL-4, IL-6, IL-7, IL-9, IL-10, IL-11, IL-13, IL-15, IL-19, IL-20, IL-21, IL-22, IFN-α, IFN-β, IFN-γ
JAK2	STAT1–6	IL-3, IL-5, IL-6, IL-10, IL-12, IL-13, IL19, IL-20, IL-22, IL-23 IFN-γ, EPO, TPO, G-CSF
JAK3	STAT1–3, 5, 6	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21
Tyk2	STAT1–4, 6	IL-6, IL-10, IL-11, IL-12, IL-13, IL-19, IL-20, IL-22, IL-23, IFN- α, IFN-β

Abbreviations: EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; TPO, thrombopoietin.

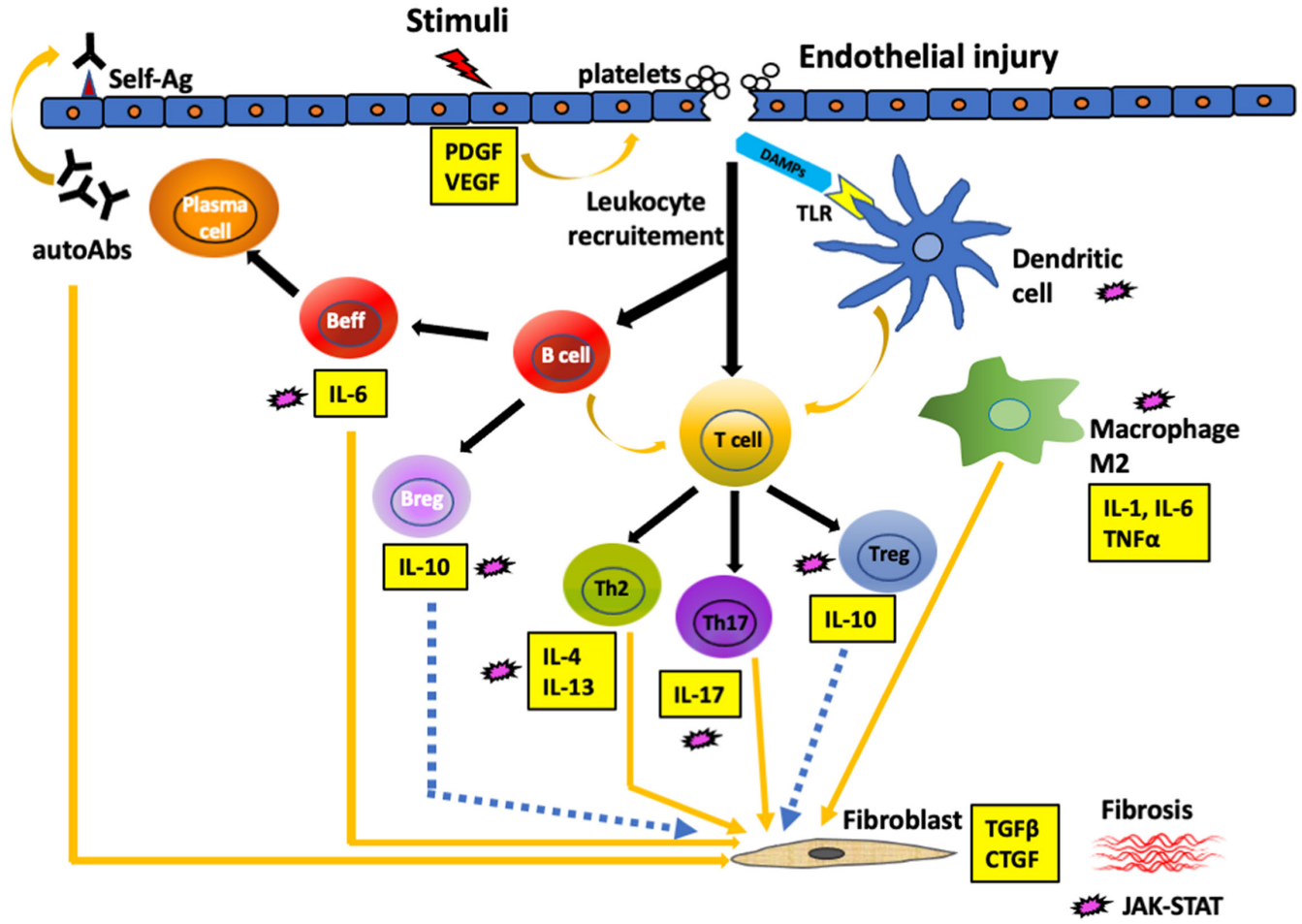

FIGURE 1 Schematic pathway showing involvement of JAK–STAT signaling on targeted cytokines and their immune cells in systemic sclerosis pathogenesis. Endothelial injury is triggered by etiological stimuli and the recruitment of leukocytes to the site of injury. Dendritic cells present antigens (Ag) to T cells upon binding of DAMPs to TLRs and innate cells activate T and B cells to differentiate into effector cells (Th2, Th17, and Beff) and plasma cells potentiating immune responses through the production of fibrogenic cytokines and autoantibodies (autoAbs). Regulatory T and B cells that have inhibitory roles are reduced. When stimulated by Th2 cytokines, macrophages differentiate into M2 macrophages producing inflammatory and profibrotic cytokines that further enable endothelial injury, and stimulate fibroblasts to establish fibrosis of the skin, lungs, and internal organs. Targeting the JAK–STAT pathway has the potential to impact the signaling of multiple innate and adaptive immune cell cytokines associated with fibrosis.

TABLE 2 Usage of JAK–STAT signaling by key cytokines in SSc and their downstream effects.[67,68,77–79]

Cytokine	JAK	STAT	Effects
TGF-β	JAK2	STAT3	Profibrotic, CTGF stimulation, collagen production
PDGF	JAK2	STAT1	Proinflammatory, ECM synthesis
VEGF	JAK2	STAT3	Profibrotic, angiogenesis
IL-6	JAK1, 2, Tyk2	STAT3	Proinflammatory, fibroblast differentiation, collagen accumulation
IL-10	JAK1, 2, Tyk2	STAT1, 2	Anti-inflammatory
IL-4	JAK1, 3	STAT6	Th2 polarization
IL-13	JAK1, 2, Tyk2	STAT6	Th2 polarization
IL-17	JAK2	STAT3	Th17 polarization

reportedly reduces dermal fibrosis by reducing TGF-β and IL-17 levels.[72] Hence, a phase I/II study of tofacitinib in patients with diffuse cutaneous SSc is currently ongoing. In vitro, selective JAK2 inhibitors reduce collagen in SSc fibroblasts. JAK2 is activated in a TGF-β-dependent manner, and its inhibition decreases the release of collagen from SSc fibroblasts, thus preventing fibrosis

TABLE 3 JAK selectivity, dosage, and safety of approved JAK inhibitors currently studied in SSc.[68,77,80]

JAK inhibitor	Selectivity	FDA indication	Dosing	Adverse effects
Tofacitinib (1st generation)	JAK1, 3>JAK2, Tyk2	RA, PsA, JIA, UC (2012)	Oral 5–10 mg BD/topical	Infection, neutropenia, hypercholesterolemia, lymphoma and other malignancies, thrombosis, GI perforation, and the elevation of LFT and creatinine
Ruxolitinib (1st generation)	JAK1, 2	PCV, MF, GVHD (2011)	Oral 5–25 mg BD/topical	Infection, anemia, neutropenia, thrombocytopenia, hypercholesterolemia, non-melanoma skin cancer, and the elevation of LFT
Baricitinib (1st generation)	JAK1, 2	RA (2018)	Oral 2 mg QD	Infection, neutropenia, hypercholesterolemia, lymphoma and other malignancies, thrombosis, GI perforation, and the elevation of LFT and blood creatinine kinase
Peficitinib (2nd generation)	JAK3, 1>JAK2, Tyk2	RA approved in Japan (2019)	Oral 150mg QD	Infection, nasopharyngitis, lymphopenia, GI perforation, sepsis, and the elevation of blood creatine kinase

Abbreviations: BD, twice daily; GI, gastrointestinal; GVHD, graft-versus-host disease; JIA, juvenile idiopathic arthritis; LFT, liver function test; MF, myelofibrosis; PCV, polycythemia vera; PsA, psoriatic arthritis; QD, once daily; RA, rheumatoid arthritis; UC, ulcerative colitis.

in preclinical models.[73] The JAK1/2 inhibitor, ruxolitinib, blocks circulating follicular T cells via the IL-21 pathway and decreases plasmablasts and immunoglobulin production in SSc patients.[74] Peficitinib, a pan-JAK inhibitor, reduces lymphocyte activation as well as cytokine and chemokine production in mononuclear cells and skin fibroblasts.[75] Meanwhile, in a recent pilot study, the JAK1/2 inhibitor, baricitinib, was found to reduce skin fibrosis and digital ulceration in SSc patients.[76]

The pharmacological effects of various JAK inhibitors differ depending on which specific cytokines are inhibited. Multiple JAK inhibitors that are currently being investigated in SSc studies, as well as their approved clinical utility for autoimmune diseases, route of administration, dosage, and safety profiles are listed in Table 3. Despite the systemic side effects, oral or topical administration is well-tolerated, and their side effects rapidly return to normal after discontinuation. However, long-term treatments of SSc with systemic steroids and biologics are associated with more life-threatening side effects, such as adrenocortical insufficiency and immunologic side effects, resulting in both disease and treatment burden in patients. Therefore, the superiority of JAK inhibitors over other agents allows clinicians to offer safer and well-established treatments to patients with SSc as they act rapidly, have a shorter half-life, can be easily administered by the oral route, target multiple cytokines, and have low immunogenicity.

5 | CONCLUSION

SSc is a highly heterogenous and complex prototypic disease that involves dysregulation of several type I and II cytokines. These proangiogenic, proinflammatory, and profibrotic cytokines, directly and indirectly, use the JAK–STAT pathway mediating pathogenic responses in the innate and adaptive immune responses. Considerably, anti-cytokine therapy targeting multiple cytokines will be more effective than those targeting a single cytokine. Nevertheless, there seems to be uncertainty regarding the selection between non-selective and selective JAK inhibitors in outweighing the risks and benefits. For instance, will single JAK inhibition only affect certain selective cytokines while ignoring others involved in SSc? Otherwise, without selective inhibition of certain JAKs, will more serious untoward effects occur? For example, will broad coverage with pan-JAK inhibitors with low selectivity for JAK-2, and those that are hematogenic toward RBC and platelets, be appealing for future therapeutic outcomes? Further research comparing non-selective and more selective JAK–STAT inhibition, comparing its use alone or in combination with other immunomodulating agents, or blocking the corresponding transcription factors will provide a platform for the development of therapeutic strategies for SSc. Although many new cytokine targets are emerging, the JAK–STAT pathway and its inhibition herald potential therapeutic targets that affect multiple cytokines and cytokine signaling pathways in reversing the fibrogenic pathology in patients with SSc.

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CONFLICT OF INTEREST

The authors declare no relevant conflict of interest.

ETHICS STATEMENT

Approval of the research protocol: No human participants were involved in this study.

Informed Consent: N/A.

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DATA AVAILABILITY STATEMENT

The datasets generated and analyzed are available for the corresponding authors on reasonable request.

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