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Review Article

Translating research to clinical application: The utilization of JAK inhibitors in scleroderma

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ABSTRACT

The clinical characteristics and prognosis of scleroderma (SSc), an uncommon autoimmune disease, can vary widely. There is no specific treatment for SSc. Medications used for the treatment of SSc, such as tocilizumab, cyclophosphamide, mycophenolate mofetil, and nintedanib, have a range of potential side effects. More than 50 ligands have been shown to activate the *JAK/STAT* signalling pathway, which plays a role in cell signal transmission through an evolutionarily conserved mechanism. The pathway of *JAK/STAT* signalling contributes to autoimmune. *JAK* inhibitors are tiny compounds with various molecular configurations. Patient illness development is only slightly slowed down or stabilised when these medications are used. In animal models of SSc, *JAK* inhibitors decreased pulmonary and cutaneous fibrosis. There are only few clinical studies on the effectiveness and safety of *JAK* inhibitors in individuals with SSc. In particular, tofacitinib and baricitinib are used for treating SSc. The reduction in the modified rodnan skin score after treatment initiation was more significant in patients with previously untreated SSc. *JAK* inhibitors may be a safe and effective treatment option for skin fibrosis and interstitial lung disease in SSc. This review examines the application of JAK inhibitors in scleroderma, encompassing both fundamental research and clinical investigations. In the future, JAK inhibitors may serve as a prospective treatment for SSc; nonetheless, the paramount consideration remains the patient's well-being and quality of life. The realization of this part will be contingent upon the completion of clinical trials.

Keywords: SSc, *JAK* inhibitors, Treatment

INTRODUCTION

Scleroderma also known as systemic sclerosis (SSc), is an autoimmune, complex, heterogeneous, and rare disease that is mainly characterised by the dysregulation of the immune system, fibrosis, and vascular damage (vasculopathy), which negatively affect patients' quality of life (Perelas, Silver & Arossi, 2020; Sobanski et al., 2019). The modified Rodnan skin score (mRSS) for skin fibrosis in patients with SSc is the most widely used clinical measure. In the clinic, 30% of patients with SSc have other complications, such as internal organ fibrosis and interstitial lung disease (ILD). One of the causes of death in patients with SSc is ILD (Pokeerbux et al., 2019; Tashkin et al., 2006).

Unfortunately, the effects of treatments for SSc (e.g. nintedanib, mycophenolate mofetil, cyclophosphamide and tocilizumab) are quite limited. The use of these drugs results in only stabilising or minor reducing of disease progression in patients (Distler et al., 2019; Hu, Li & Fu, 2021; Tashkin et al., 2016).

Janus kinase inhibitors (JAKi), which have been candidates for clinical use in SSc for the past few years, represent a new and promising class of therapeutics. They are used in the therapy for other autoimmune diseases, connective tissue diseases, and cancers.

Janus kinase (JAK) / signal transducer and activator of transcription (STAT) pathway

The *JAK/STAT* signalling pathway has evolutionary conserved roles in cell signal transduction, and more than 50 ligands activating it were reported (Hu et al., 2021). The *JAK/STAT* signalling pathway (Darnell, Kerr & Stark , 1994) plays a role in autoimmunity during investigation of interferon (IFN) signalling, and IFN-specifically was implicated in the pathology of SLE and RA.

Structurally related cytokines and some hormones are the initiation factors of the *JAK/STAT* signalling pathway cascade. The extracellular binding of these ligands to their cognate transmembrane receptors initiates the *JAK/STAT* signalling cascade (Leonard & O'Shea, 1998).

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Initiation of the *JAK/STAT* signalling pathway begins with transactivation of receptors and receptor-bound *JAKs* that catalyse tyrosine phosphorylation (*p-Tyr*) of STATs, resulting in the formation of STAT heterodimers that translocate to the nucleus and direct gene transcription. Interferons induce by the *STAT1, STAT2*, and *IRF9* complex (Leonard & O'Shea, 1998).

In all mammals, there are *JAK-1, JAK-2, JAK-3*, and *Tyk-2* composed of seven homology domains (JH) organised in 4 major structural domains: the first is the FERM domain (JH5, JH6, JH7), which mediates interaction with receptors and supports kinase function; the second is the SH2-like domain (JH3, JH4), which mediates interaction with receptors; the third is the pseudokinase domain (JH2), which regulates kinase activity; and the fourth is the kinase domain (JH1) (Figure 1). *JAK-1* and *JAK-2* are activated by many cytokines and are critical for intracellular signal transduction. *JAK-3* and *TYK-2* activite relatively few cytokines (Harrison, 2012; Seif et al., 2017).

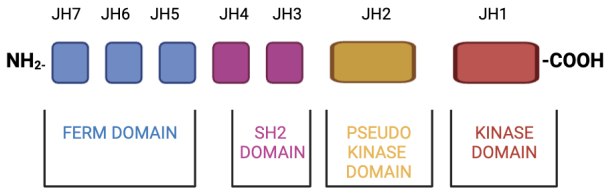

Figure 1. Domain structure of JAKs

There are also non-canonical *JAK/STAT* signalling pathways; Here, unphosphorylated *STAT* is localised on heterochromatin in association with HP1 in the nucleus. Increasing *STAT* phosphorylation significantly reduces the amount of unphosphorylated STAT localised on heterochromatin. The *JAK/STAT* signalling pathway also interferes with other signalling pathways in cells, such as *NOTC, TGF-β, NF-κB*, and PI3K/mTOR. What is important in the pathogenesis of SSc is that TGF-β profibrotic signalling regulates the JAK/STAT pathway (Aittomäki & Pesu, 2014; Mendoza, Piera-Velazquez & Jimenez, 2021). Additionally, the transcription factors *STAT* and *SMAD* from TGF-β, are sometimes included in the same transcription complex.

JAK/STAT signalling pathway negative regulators or suppressors of cytokine signalling (*SOCS*); protein tyrosine phosphatases (*PTPs*); and protein inhibitors of activated STATs (*PIASs*). These proteins are important and primary regulators of the *JAK/STAT* pathway. In fact, they act as Jack substrates that stop or block the signalling pathway (Hu et al., 2021).

JAK3 and *TYK2* germline loss-of-function (LOF) mutations are observed in autoimmune diseases and are generally considered the primary cause of disease development (Leonard & O'Shea, 1998). In addition, JAK1 somatic LOF mutations are observed in cancer cells and associated with IFN-γ resistance and cancer pathogenesis.

Gain-of-function (GOF) mutations play a role in the pathogenesis of systemic autoimmunity, particularly in *JAK-1*, polycythaemia vera (JAK2 kinase-like domain), lymphoma, leukaemia, and other cancers.

JAK inhibitors (JAKi)

JAKi are small molecules with different chemical structures. All *JAK* inhibitors exert their therapeutic effects through two distinct mechanisms. First, *JAK* inhibitors are used as immunosuppressors because the inhibition of *JAK* function reduces the levels of proinflammatory cytokines, which are increased by disease. Second, they enable the treatment of some myeloproliferative diseases and cancers in which gain-of-function JAK mutants have been identified and JAKi have successfully inhibited them (Gadina et al., 2020).

First-generation JAKis, such as baricitinib, tofacitinib, oclacitinib, ruxolitinib), are adenosine triphosphate (ATP)-competitive compounds binding to pseudokinase and kinase domains. Due to the structural similarity of these domains, these JAKi inhibit all JAK, but newer agents (such as upadacitinib) act via allosteric mechanisms (such as targeting the kinase-like domain) (Shawky, Almalki & Abdalla, 2022). Additionally, first generation of JAKi are adenosine triphosphate (ATP) competitive compounds. All of them targeted the active conformation of the tyrosine kinase domain (JH1) with a highly conserved ATP-binding pocket structure. Therefore, first-generation JAK inhibitors target multiple JAK members (Shawky et al., 2022). Therefore, they are also called pan-JAK inhibitors. Most next-generation JAKi are also ATP-competitive. However, some JAKi (e.g. Deucravacitinib) also target the JH2 domain of JAK (Shawky et al., 2022).

For the signal transduction of cytokines, *JAK-1* and *JAK-2* are critical, whereas *JAK-3* and *TYK-2* are activated by relatively few cytokines, and the selective inhibition of each might lead to fewer side effects. Thus, next-generation *JAKi* have been developed and are already used for rheumatic diseases, such as nilotinib and upadacitinib. Ritlecitinib was designed and found to be a selective *JAK-3* inhibitor (Chen et al., 2022).

AG-490i was first used in 1996 as a *JAK2* inhibitor with antileukemic activity (Shawky et al., 2022). Ruxolitinib was the first JAK inhibitor to receive FDA approval in 2011(Shawky et al., 2022). Currently, JAKs are used as important drug targets in autoimmune diseases, and JAKi has been approved for the treatment of psoriatic arthritis, rheumatoid arthritis, myeloproliferative neoplasms, vaccine-versus-host disease, and inflammatory bowel disease (Chen et al., 2022; Shawky et al., 2022). Tofacitinib and baricitinib were the first oral JAKi approved for rheumatoid arthritis (Taylor, 2019). In 2019; three JAKi were approved for clinical use. These drugs include FDA-approved lenvatinib and upadacitinib, whereas peficitinib has already been approved for rheumatoid arthritis in Japan. In

2020, delgocitinib and nilotinib were approved in Japan for the treatment of atopic dermatitis and rheumatoid arthritis, respectively (Shawky et al., 2022).

Serious adverse events are always a concern during clinical use of JAKi and require close monitoring. All JAK inhibitors have side effects such as hyperlipidaemia, cytopenia, and infection. Although tofacitinib and baricitinib have been approved for the treatment of rheumatoid arthritis after 10 and 5 years of clinical experience, respectively, they are still suspected to cause serious diseases such as malignancies and infections.

JAKi in the SSc

JAKi as a treatment for skin and musculoskeletal involvement

Dermal collagen deposition is significantly increased in bleomycin-induced SSc models. In the JAK-2 inhibitor group administered to a mouse model of SSc, a >70% reduction in dermal thickness was observed. With increasing JAK-2 inhibitor doses, dermal thickening in bleomycin-injected mice almost reached the same level as that in the control group (Dees et al., 2012).

The efficacy and effects of tofacitinib, a JAK inhibitor targeting JAK-1 and JAK-3, and ruxolitinib, a JAK inhibitor targeting JAK-1 and JAK-2, on dermal thickness were examined in an SSc model (Damsky et al., 2020). Decreased skin thickness was observed in both the tofacitinib and ruxolitinib groups (Damsky et al., 2020). Additionally, in addition to preclinical studies, tofacitinib and ruxolitinib show promise in a mouse model of interstitial lung fibrosis; This result suggests that the treatment of JAKi has a broad antifibrotic effect (Lescoat et al., 2020). According to one study, baricitinib improved the experimental SSc model lung and skin tissues in the experimental SSc model, leading to positive treatment effects. The results of immunohistochemistry demonstrated that BAR decreased the expression of *COL1A1* and *COL1A2*. BLM-induced skin and lung fibrosis improves after treatment with JAK 1-2 selective BAR at radiological, pathological, and molecular levels (Gulle et al., 2023).

As a result of the literature review, researchers performed a literature review of patients with SSc defined by the 2013 ACR/EULAR criteria and treated with JAK inhibitors by searching the Medline, Cochrane Library, and Embase databases. They included 59 (mean age 47±15 years) patients with SSc in the study. The average treatment duration of the included patients was 12 months. They were treated with JAK inhibitors (tofacitinib in 47 patients and baricitinib in 12 patients). Overall, a significant cutaneous response (>5 points on mRSS–modified Rodnan skin score and ≥25% reduction from baseline) was reported in 52 patients (88%). Additionally, among patients with ILD (n = 31), there was no disease progression. Additionally, disease progression was reported in only 2 patients during the study. Cutaneous responses were observed more frequently in treatment-naïve SSc patients. The reduction in mRSS after treatment initiation was more significant in treated patients with SSc (Moriana, Moulinet & Jaussaud et al., 2022).

Additionally, in studies on SSc, there is a role for transforming growth factor (*TGF*)-β, especially in the development of fibrosis. *TGF*-β promotes myofibroblast turnover, fibrosis, and therefore collagen deposition (Dees et al., 2012; Delany & Brinckerhoff, 1993; Xiao et al., 2008).

JAKi as a treatment for interstitial lung disease

Recently, a study demonstrated that ruxolitinib inhibited proinflammatory (M1) and profibrotic (M2) macrophages in vitro and ameliorated cutaneous and pulmonary fibrosis in a mouse model of SSc (Lescoat et al., 2020).

Aung et al. showed in a mouse model of bleomycin-induced SSc, tofacitinib, a JAK inhibitor, ameliorated cutaneous and pulmonary fibrosis with reduced Th2 and Th17 responses in the skin, IL-6-producing B lymphocytes, tissue macrophages, extracellular matrix, and profibrotic cytokine expression in the lungs (Aung et al., 2021).

Additionally, a study called SCLEROJAKI conducted in France is investigating the effect of JAK inhibitors against interstitial lung disease-related SSc (NCT05177471).

JAKi in vasculopathy treatment

SSc is a chronic and diverse connective tissue disease characterised by vascular injury (vasculopathy), immune response dysregulation linked to autoimmunity, and fibrosis development. JAKi were also proposed to have a possible function in the management of digital ulceration in a few of the examined studies, possible impact on the disease's vasculopathic component as well.

Inhibitors of JAK1 and JAK2 have been shown to alleviate skin fibrosis, and the oral JAK1/2 inhibitor baricitinib represents a potentially effective treatment for patients with diffuse cutaneous systemic sclerosis (dcSSc) exhibiting skin fibrosis and digital ulcers (DU). Baricitinib tolerated by most participants in this study. However, further large-scale clinical trials are required to validate these preliminary findings (Hou et al., 2022; Jerjen, Nikpour & Krieg, 2022).

In a study of SSc peripheral blood mononuclear cells, the pan-JAK inhibitor peficitinib was administered, and decreased *STAT-1* and *STAT-3* phosphorylation protein levels were observed (Kitanaga et al., 2020). Following favourable outcomes in patients with sclerodermatous graft-versus-host disease (GVHD) and eosinophilic fasciitis treated with ruxolitinib or tofacitinib, Deverapalli reported one of the earliest cases

of SSc treated with tofacitinib in a young patient in whom mycophenolate mofetil failed (Cao, Zhao & Hou, 2020; Hurabielle et al., 2017; Khoury et al., 2018; Kim et al., 2018; Okiyama et al., 2014).

Tofacitinib was well tolerated in the Khannas phase study; before or at week 24, no participant reported grade 3 or greater side events. The efficacy outcome measures showed a preference for tofacitinib. In subpopulations of fibroblasts and keratinocytes, baseline gene expression IFN-activated gene expression. Tofacitinib suppressed *IFN*-regulated gene expression in the basal and keratinised layers of the epidermis, as well as in *SFRP2/DPP4* fibroblasts (progenitors of myofibroblasts) and *MYOC/CCL19*, which represent adventitial fibroblasts ($p<0.05$). Tofacitinib inhibited *STAT3*, as evidenced by gene expression in DCs and macrophages ($p<0.05$). There was no clinically significant suppression of T lymphocytes and endothelial cells in skin tissue (Khanna et al., 2022).

CONCLUSION

As shown in the literature; JAK inhibitors inhibit profibrotic pathways for treating SSc and are therefore a possible treatment option. It may also show greater sensitivity and effectiveness than traditional treatments for SSc. For patients with SSc who have skin fibrosis and interstitial lung disease, particularly those who are resistant to immunosuppressive and/or immunomodulating therapy, JAK inhibitors (tofacitinib, baricitinib) may be useful. JAK inhibitors were not associated with any significant side effects in patients with SSc. Further studies are required to determine the pulmonary and long-term efficacy of JAK inhibitors in patients with SSc.

First-line therapy for refractory SSc may be successful with JAK inhibitors. The most frequent side effects that do not result in discontinuation of therapy include infections, gastrointestinal issues, elevated liver enzyme levels, and dyslipidemia. Because of their anti-inflammatory and anti-fibrotic properties, JAK inhibitors may be a potential treatment for patients with quickly progressing SSc.

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