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JANUS KINASE INHIBITORS IN SYSTEMIC SCLEROSIS: A SCOPING REVIEW

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Abstract

Systemic sclerosis (SSc) is a rare multisystemic chronic immune-mediated rheumatic disease. Although it is not common, it has the highest mortality and morbidity rate among systemic rheumatic diseases. This review aimed to analyze the results of multiple preclinical trials and clinical data on Janus kinase (JAK) inhibitors in SSc treatment and provides a comprehensive overview of JAK inhibitors as a new treatment option in SSc.

Keywords: Systemic sclerosis, JAK inhibitors, tofacitinib, baricitinib, ruxolitinib

INTRODUCTION

Systemic sclerosis (SSc) is a rare multisystemic chronic immune-mediated rheumatic disease characterized by heterogeneous manifestations of vasculopathy and fibrosis (1). Fibrosis and vasculopathy are closely related and lead to heterogeneous clinical manifestations with variable prognoses (2). Fibrosis of the skin and internal organs leads to structural deterioration and ultimately organ dysfunction. On the other hand, vasculopathy causes Raynaud phenomenon, digital ulcers, pulmonary artery hypertension, and renal crisis (2). These heterogeneous organs influence the results with considerable variability in the phenotypic manifestations, rate of disease progression, and response to therapy. Although SSc is not a common disease, it still has the highest mortality and morbidity rate among the systemic rheumatic conditions (3,4). The treatments we apply in SSc patients today are not sufficient to prevent the progression of fibrosis. Because of this, several other agents are needed for treating SSc, and recently, important breakthroughs have been made in the area of targeted therapies. Janus kinase (JAK) proteins and the Signal Transducers and Activators of Transcription (STAT) signaling pathway are among these targets.

JAKs are members of the intracellular, non-receptor protein tyrosine kinase (TYK) family, which comprises four members: JAK1, JAK2, JAK3, and TYK2 (5). These kinases bind to transmembrane cytokine receptors and initiate signaling cascades that activate transcription factors such as STAT proteins. JAKs play a role in various physiological processes, including cell proliferation, differentiation, apoptosis, immune regulation, and hematopoiesis (6). Dysregulation of JAK activity has been implicated in the pathogenesis of various immune-mediated and inflammatory diseases and cancer (6).

The JAK-STAT pathway plays a key role in the pathogenesis of SSc by activating fibroblasts and profibrotic macrophages, which initiate the process of fibrosis through various cytokines and mediators, such as interleukin (IL)-6, tumor growth factor (TGF)-β and platelet-derived growth factor (PDGF) (7,8). Preclinical studies have shown that in SSc model mice, the JAK/STAT pathway has a crucial role in cell differentiation, extracellular matrix

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remodeling, and fibrosis (9). Bellamri et al. (10) showed that ruxolitinib, a non-selective JAK inhibitor, has antifibrotic effects in the skin and lung of SSc model mice *in vivo* and in human lung fibroblasts *in vitro*. And Karatas et al. (11) showed that tofacitinib (TOFA), a potent inhibitor of JAK1 and JAK3, improves skin thickness and fibrosis in SSc model mice. These and several other *in vivo* and *in vitro* studies made it necessary to design clinical trials to show that JAK inhibitors would be beneficial for the treatment of fibrosis in SSc patients. Therefore, JAK inhibitors, which are new orally administered therapeutic agents, may prevent or slow the progression of SSc.

In this review, we provide a comprehensive overview of the preclinical and clinical trials of JAK inhibitors for SSc treatment.

Preclinical Studies of JAK Inhibitors for SSc

The exact pathogenesis of SSc has not yet been fully understood, but the main pathology involves the dysregulation of inflammation, vasculopathy, and fibrosis, which results in skin thickening and organ failure. Several studies have been conducted to elucidate the pathogenesis of SSC, and we know from recent studies that one of the target mechanisms is the JAK-STAT pathway. We already know that the JAK-STAT pathway has a key role in inflammation, and JAK inhibitors have been approved for the treatment of some inflammatory diseases such as rheumatoid arthritis (RA) and spondyloarthropathic. Recent preclinical studies showed that in SSc model mice, the JAK-STAT pathway also has a crucial role in fibrosis (9). Dees et al. (12) showed higher JAK activity in dermal fibroblasts from skin samples of SSc patients compared with healthy participants, and these results were also observed in cell cultures. To evaluate the TGF-β effect at JAK activity, they treated the healthy dermal fibroblast cultures with TGF-β. This experiment showed that treatment of healthy human dermal fibroblast cultures with TGF-β increased the JAK/STAT activity. Subsequently, they performed another study in which they treated dermal fibroblast cultures incubated with TGF-β, with JAK-2 inhibitors and they observed reduction of TGF-β target gene mRNA expression and decrease of TGF-β-induced collagen I production. On the other hand, in the healthy cultures that had not been incubated with TGF-β, the level of collagen mRNA or collagen protein did not change with JAK-2 inhibitor treatment. All these experiments showed that the JAK-STAT pathway plays an important role in the development of fibrosis, but this effect is TGF-β dependent (12). After *in vitro* studies, Dees et al. (12) established an *in vivo* bleomycin (BLM)-induced SSc mouse model and showed higher JAK activity in BLM-induced mice compared with wild-type mice. Additionally, JAK-2 inhibitors resolved dermal thickening in BLM-induced mice, and this effect was dose dependent (12). In another study, Aung et al. (13) had BLM-induced SSc mice *in vivo* and they injected intraperitoneal TOFA (20 mg/kg) 3 times per week from days 0-28. They showed that in addition to the anti-inflammatory effects, TOFA downregulated the mRNA expression of profibrotic cytokines in both the skin and lungs.

In another study, Lescoat et al. (9) compared the anti-inflammatory and anti-fibrotic effects of three JAK inhibitors, ruxolitinib (JAK2/1 inhibitor), TOFA (JAK3/2 inhibitor), and itacitinib (JAK1 inhibitor), *in vitro* on human monocyte-derived macrophages. All three JAK inhibitors had anti-inflammatory effects by decreasing the production of pro-inflammatory cytokines in M1 macrophages, but the effect of downregulating pro-fibrotic M2 macrophages was higher with ruxolitinib and TOFA, which inhibit JAK2. In addition, ruxolitinib (JAK2/1 inhibitor) represses the upregulation of proinflammatory M1 and profibrotic M2 markers in mouse macrophages in a model of HOCl-induced interstitial lung disease (ILD) (9).

From all these preclinical studies, JAK inhibitors were considered as a targeted treatment option for SSc patients in the future.

Clinical Studies of JAK Inhibitors for SSc

In 2014, Okiyama et al. (14) showed that TOFA is effective in the prevention and treatment of mucocutaneous lesions in a CD8 T-cell-mediated model of graft-versus-host disease (GVHD) mice. In a multicenter retrospective study from Europe and the United States, in steroid-refractory acute and chronic GVHD patients, ruxolitinib was shown to be more effective in both groups compared with the other second-line therapies (15). In another study on 12 steroid-refractory sclerodermatous chronic GVHD patients treated with ruxolitinib for 1 year showed a partial improvement in skin softness in 8 of the 12 patients (16). Following the results showing that JAK inhibitors improved mucocutaneous lesions in GVHD patients, several morphea and eosinophilic fasciitis (EF) cases treated with JAK inhibitors were published. In a case series of five hypereosinophilic syndrome patients with cutaneous involvement treated with either ruxolitinib or TOFA, four of these patients had remission with one of these JAK inhibitors (TOFA or ruxolitinib) without steroid requirement (17). In addition, there have been case-based articles showing that morphea had been treated successfully with TOFA (18,19).

With respect to the fibrosing nature of morphea and EF, and the JAK inhibitors to improve the fibrosis in these two diseases, suggests they might also hold promise as a treatment option for SSc. Based on this hypothesis, several studies have been progressing to evaluate the effect of JAK inhibitors in patients with SSc.

In a pilot trial, 66 patients with SSc were divided into two groups: 33 of them received oral TOFA 5 mg twice daily; and the remaining 33 received 10 mg weekly oral methotrexate (20). Skin thickness was assessed clinically [Modified Rodnan skin score (mRSS)] and ultrasound before the treatment and at weeks 26 and 52 in both groups. Before the treatment, median scores were similar in both groups, but in the TOFA group, significantly lower medians were observed at 26 and 52 weeks. Four severe adverse events were recorded during the trial, and one of them was in the TOFA group who developed progressive interstitial lung disease.

In another phase I/II double-blind, placebo-controlled trial, 15 early diffuse cutaneous SSc patients received TOFA (5 mg) twice a day or placebo (21). A skin biopsy was performed on each participant at the beginning and at week 12. They showed the inhibition of interferon (IFN)-regulated gene expression in SFRP2/DPP4 fibroblasts (progenitors of myofibroblasts) and in MYOC/CCL19 fibroblasts (adventitial fibroblasts) by TOFA, which targeted INF. At 24 weeks, mRSS was significantly improved in the TOFA group, and safety analysis showed no severe adverse events with TOFA.

Another pilot, single-center study was conducted in diffuse cutaneous SSc (dcSSc) patients. You compared 10 TOFA-treated patients that were all refractory to conventional immunosuppressants with 12 dcSSc patients who were all treated with cyclophosphamide (CYC) or mycophenolate mofetil (MMF) along with low or medium doses of steroids (22). All patients' baseline mRSS were similar and >10. After a 6-month follow-up, skin thickening was reassessed with mRSS, and eight TOFA-treated patients met the response criteria. One of the remaining patients' skin thickening was improved as well; however, it did not meet the criteria. The last one did not respond to the treatment. When compared with CYC/MMF-treated patients, mRSS significantly improved after TOFA treatment. There were no severe adverse events in TOFA-treated patients.

In a case report from the University of Tokyo, Komai et al. (23) treated a SSc patient suffering from polyarthritis who had been previously treated with methotrexate, abatacept, and tocilizumab with TOFA 5 mg daily. During treatment, at day 28, along with a decrease in the patient's Disease Activity Score 28, they also observed a significant improvement in nailfold capillary findings and mRSS.

There are also much case-based review data in the literature. Moriana et al. (24) analyzed these data to evaluate the efficacy and safety of JAK inhibitors in SSc patients. They analyzed 59 patients from clinical trials and case reports, including some trials mentioned above. Among these 59 patients, 47 were treated with TOFA, and 12 with barricitinib. The analysis showed that 52 patients had significant cutaneous response and twenty eight of 31 ILD patients did not experience progression after treatment with TOFA. Only two patients had worsened, one with skin fibrosis and the other with ILD. In addition, no severe adverse events were described in these 59 patients.

Safety

Currently, five JAK inhibitors, TOFA (JAK1/3), baricitinib (JAK1/2), peficitinib (pan-JAK), upadacitinib (JAK1), and filgotinib (JAK1), have been approved for rheumatoid arthritis treatment, and they have been approved in phase 3 clinical trials for other diseases, such as psoriatic arthritis, ankylosing spondylitis, and axial spondyloarthritis.

In 2012, after TOFA was approved by the Food and Drug Administration (FDA), the agency designed a post-marketing clinical trial, the ORAL Surveillance. ORAL Surveillance was the FDA-mandated post-marketing phase IIIb-IV study, which enrolled 4,362 patients with RA aged >50 years who had at least one cardiovascular risk factor (25). As a result, major adverse cardiovascular events and cancers occurred more often with TOFA than with a tumor necrosis factor inhibitors (TNFi) in this trial that included patients with RA who were 50 years of age or older and had at least one additional cardiovascular risk factor. This analysis also revealed a higher risk of no serious infections and herpes zoster with TOFA versus TNFi and a higher risk of serious infections with TOFA 10 mg two times per day versus TNFi, particularly in patients aged ≥65 years (26).

After ORAL Surveillance, FDA alerted on JAK inhibitors and there had been several clinical trials with TOFA and other JAK inhibitors, but they showed that the risk of malignancy and cardiovascular events was similar with the TNFi in contrast to ORAL Surveillance (27). All trials have mentioned JAK inhibitors with good safety profiles. However, further studies are needed.

In SSc, JAK inhibitors seem to be an optional treatment now, so there is no safety trial with JAK inhibitor treatment yet, but case-based reports showed no serious adverse events. Long- term and large clinical trials are still needed to be conducted.

DISCUSSION

Preclinical studies have shown that the JAK/STAT pathway has a crucial role in inflammation, cell differentiation, extracellular matrix remodeling, and fibrosis with various cytokines and mediators, such as IL-6, TGF-β and PDGF. Besides the anti-inflammatory effects that have been recently shown, JAK inhibitors, especially JAK2 inhibitors, improve fibrosis by decreasing the pro-fibrotic M2 macrophage marker. Preclinical

trials have also shown that JAK inhibitors improve skin thickness and ILD in a mouse model of SSc.

There have been several small, single-center, case-based, pilot trials and case reports on the treatment with JAK inhibitors in SSc patients. They all showed that JAK inhibitors improved skin thickening, arthritis, and ILD symptoms in SSc patients. There had been no severe adverse events observed in these JAK inhibitor-treated SSc patients.

It is already recognized that SSc is a chronic multisystemic disease with heterogeneous manifestations by different pathological conditions such as vasculopathy, inflammation, and fibrosis, but the exact pathogenesis remains unknown. Therefore, the treatments we apply in SSc patients today are not sufficient to prevent progression of fibrosis. SSc still has a high mortality and morbidity rate.

However, these preclinical trials showed that because of the different multiple pathological conditions such as vasculopathy, inflammation, and fibrosis play a role in SSc pathogenesis, JAK inhibitors, which play a crucial role in these pathways, may be a good option in SSc patients' treatment. In addition, the case-based trials show that JAK inhibitors work in SSc patients and it seems safe and well tolerated. Indeed, JAK inhibitors may be an effective treatment option in SSc, but more new clinical trials are needed.

Footnote

Authorship Contributions

Concept: F.B., M.B., Design: F.B., M.B., Literature Search: F.B., M.B., Writing: F.B., M.B.

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