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 prognosis (2). Fibrosis of 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 results with considerable variability in the phenotypic manifestations, the 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 diseases. This review aimed to analyze the results of multiple preclinical trials and clinical data about 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
matrix remodeling, and fibrosis (9). Bellamri et al. (10) showed that ruxolitinib, a nonselective JAK inhibitor, has antifibrotic effects in the skin and lung of SSC model mice in vivo and in human lung fibroblasts in vitro. And also Karatas et al. (11) showed that tofacitinib, 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 the JAK inhibitors would be beneficial for the treatment of fibrosis in SSC patients. Therefore, JAK inhibitors, 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 in SSC treatment.

**Preclinical Studies of JAK Inhibitors in SSC**

The exact pathogenesis of SSC has not yet been fully understood, but the main pathology is 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 have already known 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 spondyloarthropathies. 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 observed in cell cultures as well. Then, to evaluate the TGF-β effect at JAK activity, they treated 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 JAK2 inhibitors and they observed reduction of TGF-β target gene mRNA expression and also decrease of TGF-β-induced collagen-I production. On the other hand, in healthy cultures that had not been incubated with TGF-β, the level of collagen mRNA or collagen protein did not change with JAK2 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, JAK2 inhibitor resolved dermal thickening in BLM-induced mice and this effect was dose dependent. In another study, Aung et al. (13) had BLM-induced SSC mice in vivo, and they injected intraperitoneal tofacitinib (20 mg/kg) 3 times per week from day 0-28. The study showed that besides the anti-inflammatory effects, tofacitinib down-regulated 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), tofacitinib (JAK3/2 inhibitor), and itacitinib (JAK1 inhibitor), in vitro on human monocyte-derived macrophages. All three JAK inhibitors had an anti-inflammatory effect by decreasing the production of pro-inflammatory cytokines in M1 macrophages, but the effect of downregulation the pro-fibrotic M2 macrophages was higher with ruxolitinib and tofacitinib, which have JAK2 inhibition. Additionally, ruxolitinib (JAK2/1 inhibitor) represses the upregulation of pro-inflammatory M1 and pro-fibrotic M2 markers in mouse macrophages in a model of hypochlorous acid-induced interstitial lung disease (ILD) (9).

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

**Clinical Studies of JAK Inhibitors in SSC**

In 2014, Okiyama et al. (14) showed that tofacitinib is effective in the prevention and treatment of mucocutaneous lesions in a CD8 T-cell-mediated model of mucocutaneous lesions (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 five hypereosinophilic syndrome patients with cutaneous involvement treated with either ruxolitinib or tofacitinib, four of these patients had remission with one of these JAK inhibitors (tofacitinib or ruxolitinib) without steroid requirement (17). Also, there have been case-based articles showing that morphea had been treated successfully with tofacitinib (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 SSc patients. In a pilot trial, 66 SSc patients were divided into two groups, 33 of them received oral tofacitinib 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 then at weeks 26 and 52 in both groups. Before the treatment, median scores were similar in both groups but in the tofacitinib 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 tofacitinib group who developed progressive ILD.

In another phase I/II double-blind placebo-controlled trial, 15 early diffuse cutaneous SSc (dcSSc) patients had tofacitinib 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-regulated gene expression in SFRP2/DPP4 fibroblasts (progenitors of myofibroblasts) and in MYOC/CCL19 fibroblasts (adventitial fibroblasts) by tofacitinib that addressed the INF as the target of tofacitinib. At 24 weeks, mRSS was significantly improved in the tofacitinib group, and safety analysis showed no severe adverse events with tofacitinib.

Another pilot, single-center study was conducted in dcSSc patients. You et al. (22) compared ten tofacitinib-treated patients that were all refractory conventional immunosuppressants with 12 dcSSc patients who were all treated with cyclophosphamide (CYC) or mycophenolate mofetil (MMF) in combination with low or medium doses of steroids. All patients baseline mRSS were similar and >10. After 6 months of follow-up, skin thickening was reassessed with mRSS, and eight tofacitinib-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 the mRSS significantly improved after tofacitinib treatment. There was no severe adverse event in tofacitinib-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 before, with tofacitinib 5 mg daily. During the course of 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 and coworkers analyzed these data to evaluate the efficacy and safety of JAK inhibitors in SSc patients (24). They analyzed 59 patients from clinical trials and case reports that includes some trials which we mentioned above. Among these 59 patients, 47 were treated with tofacitinib, and 12 were treated with barricitinib. The analysis showed that 52 patients had significant cutaneous response and 28 of 31 ILD patients did not experience progression after treatment with tofacitinib. Only two patients had been worse, one with skin fibrosis and the other with ILD. In addition, no severe adverse events were described in these 59 patients.

Safety

Currently 5 JAK inhibitors, tofacitinib (JAK1/3), baricitinib (JAK1/2), peficitinib (pan-JAK), upadacitinib (JAK1) and filgotinib (JAK1) have been approved in RA treatment and have been approved or in phase 3 clinical trials in other diseases such as psoriatic arthritis, ankylosing spondylitis and axial spondyloarthritis.

In 2012, after tofacitinib 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. As a result, major adverse cardiovascular events and cancers occurred more often with tofacitinib than with a TNF-inhibitor (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 infection with tofacitinib versus TNFi and a higher risk of serious infections with tofacitinib 10 mg two times per day versus TNFi, particularly in patients aged ≥65 years (26).

After the ORAL Surveillance, FDA allergated on JAK inhibitors and there had been several clinical trials with tofacitinib and the other JAK inhibitors, but they showed that the risk of malignancy and cardiovascular events was similar with the tumor necrosis factor inhibitors in contrast to the ORAL Surveillance (27). All trials have mentioned JAK inhibitors with a good safety profile. But still 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 big clinical trials are still needed to be conducted.

DISCUSSION

Preclinical studies show that the JAK/STAT pathway plays a crucial role in inflammation, differentiation of cells, 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 the JAK2 inhibitors, improve fibrosis by decreasing the pro-fibrotic M2 macrophage marker. Preclinical trials also show that JAK inhibitors improve skin thickness and ILD in mouse model 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 had 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 due to different pathological conditions such as vasculopathy, inflammation, and fibrosis; however, we still do not know the exact pathogenesis; 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 the JAK inhibitors may be a good option for treatment of SSc patients, because the JAK inhibitors are playing a crucial role in pathways of different multiple pathological conditions such as vasculopathy, inflammation and fibrosis. Also, 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.

REFERENCES

