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REVIEW

Potential Use of Janus Kinase Inhibitors in the Treatment of Systemic Lupus Erythematosus

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Abstract: Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease with unclear pathogenesis. One characteristic of SLE is pro-inflammatory and anti-inflammatory cytokine imbalance. Janus kinase (JAK) is an intracellular non-receptor tyrosine kinase essential for many cytokine signaling pathways. Dysregulation of the JAK/signal transduction and transcriptional activator (STAT) pathway is an important process in SLE pathogenesis. Targeting JAK/STAT proteins can simultaneously block the functions of multiple cytokines. Current SLE treatment with non-specific corticosteroids and immunosuppressants can cause many adverse reactions. Therefore, treatments designed to control specific molecular targets for SLE are desirable. JAK inhibitors (JAKis) are a potential treatment for rheumatic diseases; however, the use of targeted signaling pathways to treat SLE remains a challenge, and its efficacy has not been determined. JAKis have shown positive results in reducing the use of glucocorticoids and/or non-specific immunosuppressants for SLE. JAKis are currently undergoing several clinical trials and expected to be the next stage in the treatment of SLE. Therefore, inhibition of the JAK/STAT pathway through JAKis may improve traditional treatment strategies for SLE.

Keywords: systemic lupus erythematosus, Janus kinase, JAK/STAT pathway, JAK inhibitors

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease that affects many organs and tissues, particularly the kidneys and skin. Its pathogenesis is complex and includes the overproduction of a series of cytokines. Under these conditions, loss of self-tolerance and overproduction of autoantibodies occur.[1] Many of these cytokines play biological roles through the JAK/STAT cascade signaling pathway. Activation of the JAK/STAT pathway enables B cells stimulated by autoreactive T helper cells to undergo a class shift and differentiate into autoantibody-producing cells in response to interleukin (IL)-21 and other cytokines. In addition, B cells produce various cytokines, such as IL-6[2,3] Analysis of JAK/STAT pathway inhibition suggested that it plays a central role in reducing inflammation in SLE.[1] Current SLE treatment regimens are usually based on corticosteroids and immunosuppressants. Corticosteroids therapy is widely used to significantly improve the prognosis of SLE, with reported survival rates of 90% or higher after 5 years, 70–90% after 10 years, and 50–70% after 20 years.[1] However, the possible occurrence of many adverse reactions and poor efficacy reflects high morbidity and mortality of SLE.[4,5] Biomolecular targeting of pro-inflammatory cytokines has improved the treatment of other autoimmune diseases;[6] therefore, the JAK/STAT pathway is an ideal target for SLE treatment.[7] Many JAKis have been studied for the treatment of SLE.1 JAKis block downstream signaling of type I/II interferon (IFN). Therefore, JAKis may have a variety of effects on cytokines and cells in the pathogenesis of SLE, including innate immune cells, B cells, CD8+T cells, and CD4+T cell subsets (helper T cells (Th), including Th1 cells and pathogenic Th17 cells).[8–10] In recent years, studies have analyzed whether inhibition of this intracellular signaling

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can play a safe and effective role in patients with SLE,[6] and some positive results have been achieved. Therefore, JAKis targeting pro-inflammatory cytokines may be a promising therapeutic strategy for SLE.

JAK/STAT Pathway

Four JAKs have been identified in mammals: JAK1–3 and non-receptor tyrosine-protein kinase 2 (TYK2). JAK1–2 and TYK2 are commonly expressed, whereas JAK3 is only expressed in hematopoietic cells.[1] The structure of JAK consists of seven homologous regions (JH1–JH7), forming four domains (FERM, SRC homology 2 (SH2), pseudokinase, and kinase domains). The JH1 and JH2 regions are located at the C-terminus of the enzyme-encoded kinase and pseudokinase, respectively. JH2 homologs are characterized by dual kinase activity and regulate catalytic kinase activity. Seven STAT proteins have been identified: STAT1–4, STAT5A, STAT5B, and STAT6.[11] STAT proteins consist of an N-terminal domain, DNA-binding domain, curling tail domain, splice domain, SH2 domain, tyramyl phosphate tail, and transactivation domain located at the C-terminal.[12,13] Each STAT field plays a unique role. The N-terminus is a conserved domain responsible for STAT phosphorylation. The DNA-binding domain forms a complex with DNA and STAT proteins, while the SH2 domain interacts with other proteins. Finally, the C-terminal domain functions as the activation center for the entire STAT molecule.[14] Protein kinases are important modulators of cell function and achieve intracellular signal transduction through the linkage between JAK, TYK2 isomers, and STAT members. JAK receives signals from various cytokine receptors that are members of the IL and IFN families.[15,16] The role of JAK in signaling is focused on type I and type II cytokine receptors, and the activity of each JAK depends on its specific interaction with the cytokine receptors.[3] The specific cytokine receptor/JAK kinase combination is important for the generation of targeted therapies.

Pathogenesis of the JAK/STAT Pathway in SLE

In SLE, immune imbalance may activate cytokines of the innate and adaptive immune system and increase the level of pro-inflammatory factors, such as type I IFN, IL-2, IL-4, IL-6, IL-13, IL-15, IL-17, IL-23, and IL-31.[17–19] These cytokines can activate the JAK/STAT pathway in immune cells (such as dendritic cells) (Figure 1), further increasing the level of pro-inflammatory cytokines and activating T and B cells. This induces T cells to release pro-inflammatory

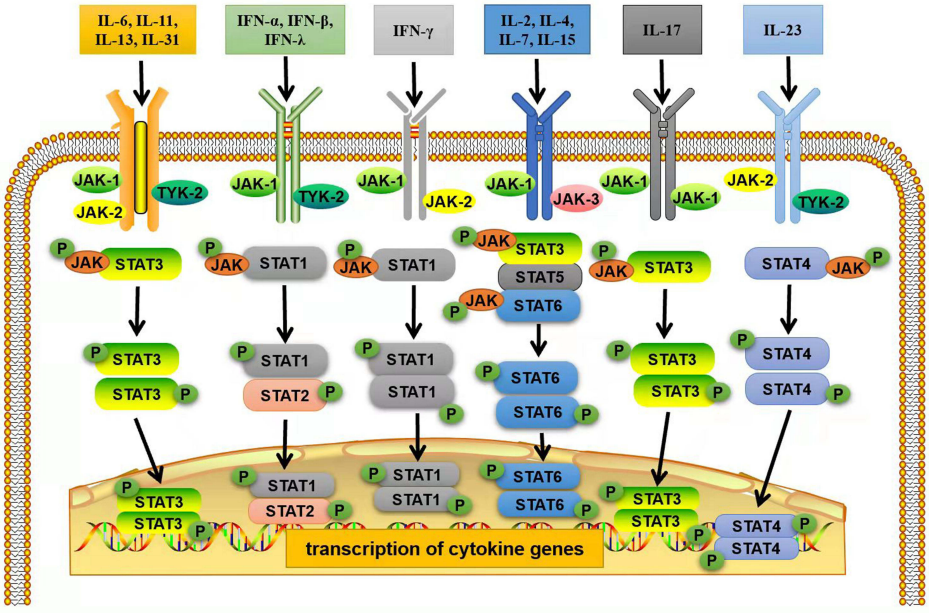

Figure 1 Mechanism of the JAK/STAT signaling pathway activation in immune cells in SLE. Extracellular cytokines bind to their specific receptors on immune cells (such as dendritic cells) to induce dimerization of JAKs, which are then activated and phosphorylated by tyrosine residues in the tail of their receptors to form p-JAK. Subsequently, these phosphorylation sites act as docking sites for STAT binding via the SH2 domain, resulting in tyrosine phosphorylation and STAT activation to form p-STAT. The phosphorylated STAT homo- or heterodimer is then translocated into the nucleus. There they act as transcription factors, regulating the expression of inflammatory cytokine genes. Adapted from Montero P, Milara J, Roger I, et al. Role of JAK/STAT in interstitial lung diseases; molecular and cellular mechanisms. *Int J Mol Sci*. 2021;22 (12):6211. Creative Commons.[23]

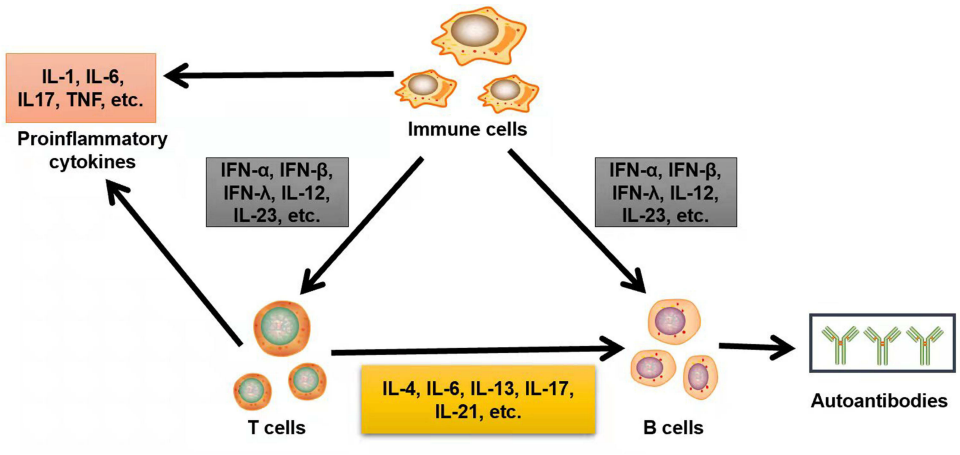

Figure 2 Mechanism of imbalance between immune cells in SLE. Activated by the JAK/STAT signaling pathway, immune cells (such as dendritic cells) can secrete a variety of pro-inflammatory cytokines, such as type I interferon, IL-12, and IL-23, and bind to specific cytokine receptors of T and B cells, resulting in their activation. Activated T cells secrete pro-inflammatory cytokines, such as IL-4, IL-6, and IL-13, and further activate B cells to secrete more autoantibodies. Immune cells and T cells activated by the JAK/STAT signaling pathway also secrete common pro-inflammatory cytokines that contribute to the inflammatory environment in SLE. Therefore, many inflammatory cytokines cause immune disorders in SLE via the JAK/STAT pathway.

cytokines and B cells to generate autoantibodies (Figure 2),[3] indicating the importance of the JAK/STAT pathway in the pathogenesis of SLE. In recent studies, IL-4, IL-6, and IL-21 have been considered potential targets for JAK inhibition in SLE.[3,20,21] Disruption of the regulation between type I IFN and B cells is one of the main features of SLE that can be targeted by JAKis.[22] The pathogenesis of SLE caused by the JAK/STAT pathway is shown in Figures 1 and 2.

Different JAKi Action Targets

JAKi is one of the newest classes of targeted synthetic disease-modifying antirheumatic drugs (TsDMARDs). JAKis are oral small-molecule drugs that can enter the cytoplasm and directly regulate intracellular signal transduction.[3] JAKis suppress many pro-inflammatory cytokines by inhibiting the JAK/STAT pathway.[3] In particular, TsDMARDs act by blocking ATP-binding sites in the JAK kinase-catalyzed region.[24,25] This inhibition of downstream signaling pathways is related to immune regulation and can also block cytokine receptor phosphorylation and gene transcription, ultimately leading to impaired differentiation of Th1, Th2, Th17, and other cells,[3,22,26] thus achieving therapeutic effects. JAKi has been extensively studied in the JAK/STAT pathway (Table 1).[3] The main target of each JAKi differs; however, there are similar adverse reactions.

The Effect of JAKi in in vitro Experiments

In vitro, T cells from patients with SLE carrying the STAT4 risk allele showed enhanced IFN-α and IL-12 phosphorylation of STAT4, leading to significant IL-12 induction of IFN-γ production in T cells. The addition of TYK2 inhibitors

Table 1 Overview of JAKis of Effect Targets and Adverse Effects

Medication	Effect Targets	Adverse Effects
Tofacitinib	Inhibits JAK1/JAK3 and, to a lesser extent, JAK2/TYK2.	Infections: upper respiratory tract infections, urinary tract infections, herpes virus reactivation (Herpes Zoster), etc.
Baricitinib	Inhibit JAK1 and JAK2.	Gastrointestinal disorders: nausea, diarrhea.
Ruxolitinib	Inhibit JAK1 and JAK2, with moderate activity against TYK2.	Blood cell count alteration: decrease in the number of lymphocytes, neutrophils, natural killer cells, and platelets.
		Blood/serum changes: elevation of liver enzymes, hyperlipidemia, increase in bilirubine, Increase in creatine phosphokinase.
		Rare adverse events: thromboembolic events, non-melanoma skin cancers, solid cancers.

Abbreviations: JAK, janus tyrosine kinase; TYK, tyrosine kinase.

prevented IL-12 and IFN-α activation in T cells, and the addition of tofacitinib to block JAK2 inhibited IFN-γ-induced cell activation.[21] In addition, Anti-double-stranded DNA(anti-ds-DNA) and anti-extractable nuclear antigens(ENA) specific antibody-secreting cells (ASCs) in blood samples from patients with SLE expressed plasma cell niche receptor cytokines, such as IL-6, which promote autoantibody production in a STAT3-dependent manner. These effects were suppressed after the addition of ruxolitinib.[27,28] Previous in vitro studies have also shown that baricitinib mitigated B cell differentiation and restored podocyte skeletal structure damaged by inflammatory stimulation by blocking the JAK/STAT pathway.[29]

The Role of JAKi in in vivo Studies

Preclinical Studies

Most studies have focused on kidney and skin lesions associated with SLE, and good therapeutic results have been achieved. With respect to lupus nephritis (LN), treatment with tofacitinib (15 mg/kg/d) improved LN in Murphy Roths Large/lymphoproliferation (MRL/lpr) mice, as evidenced by decreased albuminuria and reduced renal histopathological scores, as well as improved clinical markers (reduced plasma anti-ds-DNA antibody levels).[30] The mechanism of tofacitinib may be to relieve SLE by upregulating the expression of the TGFβI receptor and inhibiting the activation of CD4+T cells.[30] Tofacitinib treatment also reduced glomerular, tubular, and interstitial lesions and reduced IgG and C3 renal deposition in mice. At the same time, the number of T cells and macrophages and the expression of STAT regulatory genes and several inflammatory mediators were reduced. The levels of inflammatory cytokines TNF-α, IFN-α, and IL-17 were significantly reduced.[31] In another study, tofacitinib-treated MRL/lpr mice showed low levels of albuminuria, reduced frequency of severe glomerulonephritis, low glomerular scores, less pronounced interstitial nephritis, and low intensity of renal IgG and C1q deposits.[32] A study using baricitinib showed the expression of structural proteins in renal podocytes was restored, and renal inflammation improved in mice while inhibiting B cell differentiation and subsequent immunoglobulin production stimulated by pro-inflammatory conditions.[29] MRL/lpr mice usually develop cutaneous lupus erythematosus (CLE), and tofacitinib-treated mice had improved skin hyperplasia and rashes on the face and back, while pathology suggests a significant reduction in skin hyperplasia and inflammatory infiltration.[28] In addition, TREX1$^{-/-}$ mice spontaneously developed CLE-like red scales and skin lesions at a certain age, and JAK1i treatment improved skin lesions and significantly reduced lupus skin activity scores.[33] In addition, ruxolitinib reduced the development of lupus-associated skin lesions, inflammatory infiltration (as well as infiltrating T cells), and epidermal hyperplasia and downregulated the expression of IFN response genes.[34]

Clinical Research

In human SLE, tofacitinib, baricitinib, and ruxolitinib are the main drugs used for treatment and have been widely studied; therefore, these three drugs will be the focus of our discussion. For tofacitinib, 5 mg twice daily treatment in patients with SLE significantly reduced STAT phosphorylation in T cells, IFN levels in circulating immune cells, and percentage of low-density granulocytes and neutrophil extracellular trap complexes, while HDL cholesterol increased. Overall, this improved cardiac and immunological features associated with premature atherosclerosis in SLE without adverse side effects[35] In patients with “refractory” CLE, the index score for the CLE disease area and severity showed significant improvement with tofacitinib treatment.[36] In addition, tofacitinib improved arthritis and rashes in patients with SLE, but there was no significant improvement in serological markers, and varicella zoster was present in some patients.[36]

With respect to baricitinib, skin lesions improved significantly in patients with familial lupus frostbite and TREX1 mutations after treatment with 4 mg/day; however, pain associated with arthritis and skin damage was not completely alleviated, and mild respiratory infections occurred repeatedly.[37] Another study showed the refractory papuloscaly rash in patients with SLE completely resolved after baricitinib treatment.[37] In a recent study, baricitinib treatment with 4 mg/day was used to induce complete renal response (significant reduction in urinary protein levels) and control joint performance in patients with rhupus with type V glomerulonephritis.[38]

Table 2 JAKis of Clinical Trials in SLE Patients

Study [Ref.]	Disease Subtype	Drug	Number of Patients	Study Duration	Dosage of JAKi/Day	Concomitant Immuno-Suppressive Agents	Results
Hasni et al[35]	SLE	Tofacitinib	30	8 weeks + followed 4 weeks	5 mg × 2	No	It is found to be safe in SLE meeting study's primary endpoint. It also improves cardiometabolic and immunologic parameters associated with the premature atherosclerosis in SLE, high-density lipoprotein cholesterol levels and particle number; lecithin: cholesterol acyltransferase concentration, cholesterol efflux capacity, improvements in arterial stiffness and endothelium-dependent vasorelaxation and decrease in type I IFN gene signature, low-density granulocytes and circulating NETs.
You et al[40]	SLE	Tofacitinib	10	4 weeks to 12 months	5 mg × 2	Yes	Quickly and efficient amelioration of arthritis, but a partially improvement of skin rash; significantly decrease of SLEDAI-2K and PGA score, but no notable serological change; anti-dsDNA levels probably based on the varied activity of SLE.
Bonnardeaux et al[41]	CLE	Tofacitinib	3	1 to 7 months	5 mg × 2	Yes	Important improvement of CLASI score.
Wallace et al[4]	SLE/CLE	Baricitinib	314	24 weeks	2 mg/day, or 4 mg/day	Yes	Significantly more patients achieved SLEDAI-2K remission of either arthritis or rash at week 24 with a high dose of baricitinib (but not baricitinib 2 mg) compared to PBO mucocutaneous activity seen in 84% patients, but low CLASI score.
Zimmermann et al[42]	CLE	Baricitinib	3	3 months	4 mg/day	No	Notable improved cutaneousmodifications as measured by R-CLASI after 3 months; pain accompanying arthritis and skin lesions not completely remitted, in contrast to the results on cutaneous signs (one patient with complete relief of skin and joint pain, whereas in 2 patients, pain associated with joint inflammation was partially diminished as measured by VAS); inhibition of systemic type I IFN activation in blood; cold generated a stress response in patient's fibroblasts; reduction of disease flares.
Park et al[39]	SLE/DLE	Ruxolitinib	1	2 months	1.5% ruxolitinib cream	Yes	Improvement of hyperpigmented, violaceous plaques with scale and associated alopecia, subtle hair regrowth.

Abbreviations: Study ID, Study identifier; DLE, Discoid lupus erythematosus; CLE, cutaneous lupus erythematosus; SLEDAI 2K, Systemic Lupus Erythematosus Disease Activity Index 2000; BILAG, British Isles Lupus Assessment Group Disease Activity Index; PGA, Physician Global Assessment; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFN, interferon; NETs, neutrophil extracellular traps; R-CLASI, revised cutaneous lupus area and severity index; PBO, placebo; VAS, visual analog scale; anti-dsDNA, Anti-double-stranded DNA.

Table 3 Ongoing Studies on the Use of JAKis in SLE Patients are Presented

Disease	Study ID	Trial Phase Study Design	Drug	Dosage of JAKi/day	Number of Patients	Study Duration	Primary Outcome Measures
SLE/CL	NCT05048238[43]	Phase I	Tofacitinib	11 mg	10	25 days	Change in percentage of Ultraviolet B (UVB)-induced apoptotic epidermal cells [Time Frame: Day 1 to Day 26]. -The percentage of Ultraviolet B (UVB)-induced apoptotic cells at a visit is defined as the difference between the percentage of apoptotic epidermal cells in the UVB-exposed biopsy and percentage of apoptotic epidermal cells in the unexposed biopsy at the same visit

(*Continued*)

Table 3 (Continued).

Disease	Study ID	Trial Phase Study Design	Drug	Dosage of JAKi/day	Number of Patients	Study Duration	Primary Outcome Measures
LN	NCT05686746[44]	Phase 2 Phase 3	Baricetinib	4mg or 2 mg	80	Over 2 Years	1.proteins creatinine ratio [Time Frame: 3 months] nephritis 2.proteins creatinine ratio [Time Frame: 6 months] nephritis 3.proteins creatinine ratio [Time Frame: 1 year] nephritis
DLE	NCT04908280[45]	Phase 2	Ruxolitinib	1.5% cream × 2	15	12 weeks	Mean change in the severity of disease as measured by the Investigator's Global Assessment [Time Frame: Baseline to 12 weeks]

Abbreviations: Study ID, Study identifier; DLE, Discoid lupus erythematosus; CLE, cutaneous lupus; LN, Lupus nephritis.

With respect to ruxolitinib, rapid clinical improvement and almost complete regression of skin lesions have been described in patients with lupus erythematosus caused by TREX1 defects associated with Aicardi–Goutieres syndrome.[36] In a patient recently diagnosed with SLE, 1.5% ruxolitinib cream was used to treat a right scalp plaque. After two months, the plaque improved, and hair regrowth occurred,[39] suggesting that topical ruxolitinib is an effective treatment for CLE and associated hair loss. In addition, ruxolitinib effectively blocks the production of anti-ENA and anti-dsDNA antibodies in patients with SLE.[36]

Clinical study results for treating SLE with tofacitinib, baricitinib, and ruxolitinib are shown in Table 2. The main studies on ongoing clinical trials of JAKi in patients with SLE are shown in Table 3.

Conclusion

The JAK/STAT pathway is involved in the pathogenesis of SLE and associated with elevated levels of pro-inflammatory cytokines. JAKis play an immunomodulatory role in SLE by inhibiting various cytokine signaling pathways mediated by JAK/STAT. Thus, mechanism-based therapies targeting multiple cytokines and their signaling have brought about a paradigm shift in SLE treatment strategies. Current treatments are based on corticosteroids and immunosuppressants; however, some patients experience poor responses and require further treatments. Intensive and appropriate induction therapy is a prerequisite for achieving and maintaining SLE remission without causing organ damage. JAKis target the JAK/STAT pathway, reduce pro-inflammatory cytokine levels, inhibit inflammatory immune cells, and may ultimately lead to SLE disease remission without the use of corticosteroids. Clinical trials of JAKis in later stages of treatment have indicated that they may be effective for sustained remission, drug-free remission, or even cure in patients with SLE. Therefore, JAKis are a promising class of drugs for the treatment of SLE; however, more basic and clinical studies are needed to further confirm their efficacy and safety.

Disclosure

The authors report no conflicts of interest in this work.

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