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# JAKINIBS IN SYSTEMIC LUPUS ERYTHEMATOSUS: CURRENT INSIGHTS AND FUTURE PROSPECTS

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## Abstract

This review summarizes current research and data regarding the use of Janus kinase inhibitor (JAKinib) therapies in the treatment of systemic lupus erythematosus (SLE). SLE is a multisystemic inflammatory rheumatic disease that is considered the prototype of autoimmune diseases. The expanding body of knowledge concerning the disease's pathogenesis and advancements in drug technology have ushered in new treatment options and strategic approaches. JAK-signal transduction activator of transcription pathway activation is involved in the pathogenesis of several inflammatory diseases. JAKinibs were approved for the treatment of rheumatoid arthritis, psoriatic arthritis, psoriasis, alopecia, and ulcerative colitis. Jakinibs, emerge as a potential treatment option with the capacity to intervene in the pathogenesis of SLE. Their promise in SLE treatment lies in their ability to target the fundamental pathophysiological mechanisms underpinning this condition and regulate immune system responses. However, it is imperative to accumulate more comprehensive data regarding the clinical efficacy and safety of this innovative treatment approach. The thorough evaluation of this class of drugs through additional clinical trials and randomized controlled trials holds the potential to enhance the quality of life for SLE patients and positively influence the disease's course. In summary, it can be concluded that the search for new and effective treatments for SLE is ongoing, and JAKinibs are expected to play a crucial role in this quest.

**Keywords:** Systemic lupus erythematosus, JAKinibs, tofacitinib, baricitinib, upadacitinib, phase

## INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystemic inflammatory rheumatic disease that is considered the prototype of autoimmune diseases. Complex genetic interactions, hormonal factors, and environmental triggers are involved in SLE pathogenesis. During the initial years following the characterization of this disease, high morbidity and mortality rates prevailed because of the limited availability of effective treatment options. The expanding body of knowledge concerning disease pathogenesis and advancements in drug technology have ushered in new treatment options and strategic approaches (1). Among the pivotal cytokines involved in the

pathogenesis of SLE, type 1 interferon (IFN) plays a crucial role (2). A relatively recent addition to the therapeutic arsenal, Janus kinase inhibitors (Jakinibs) act by blocking the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway and have shown significant efficacy in treating various inflammatory rheumatic diseases, particularly rheumatoid arthritis (RA) (3). These orally administered molecules bind to type I and II cytokine receptors, inhibiting the intracellular response of cytokines and effectively modulating multiple cytokines implicated in the pathogenesis of SLE. Consequently, the use of Jakinibs for treating SLE has gained prominence recently (4). In this review, we summarize current research and

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data regarding the use of Jakinib therapies for treating SLE, providing valuable insights into this evolving field.

### JAK/STAT Pathway in SLE Pathogenesis

SLE presents with various abnormalities in both innate and acquired immunity, contributing to the complex pathogenesis of autoimmune and autoinflammatory changes. Within this context, numerous proinflammatory cytokines exhibit irregularities in SLE, including type 1 IFN, interleukin (IL)-2, IL-4, IL-6, IL-13, IL-15, IL-17, IL-23, and IL-31 (5). These cytokines play a pivotal role in activating the JAK/STAT pathways in dendritic cells and initiating proliferation mechanisms in T and B lymphocytes. The use of jakinib treatment strategically intervenes by blocking the JAK/STAT pathway, setting in motion a series of intricate mechanisms. This blockade effectively inhibits the activation of B cells, forming the fundamental basis for the efficacy of these drugs for treating SLE.

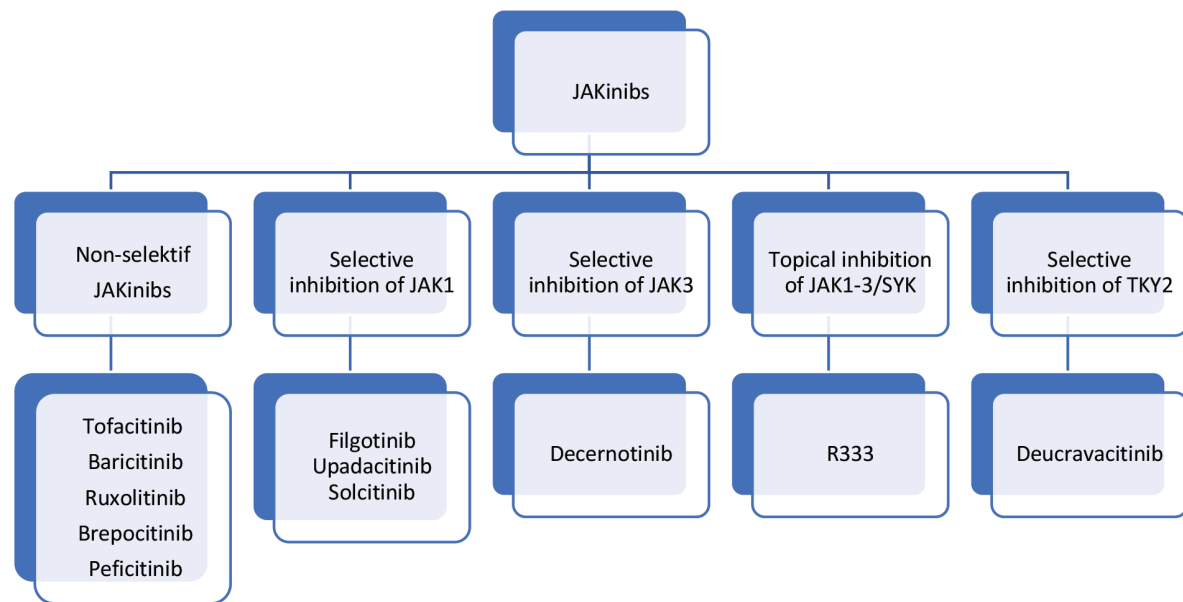
### JAK Inhibitors

Jakinibs, referred to as targeted synthetic (non-biological) disease-modifying antirheumatic drugs (tsDMARDs) within the field of rheumatology, play a pivotal role in the management of rheumatic disorders. DMARDs constitute a diverse class of therapeutic agents renowned for their dual capability to alleviate symptoms by directly intervening in the underlying pathogenic processes and to impede or slow the progression of the disease, thereby offering effective symptom control. Within this category, Jakinibs exert their influence by primarily targeting JAK proteins. JAKs constitute a family of tyrosine kinases that associate with the cytoplasmic domains of transmembrane type 1 and type 2 cytokine receptors. Upon ligand engagement, such as by cytokines or growth factors, JAKs bound to the receptor become activated, triggering receptor phosphorylation (6,7). Subsequently, this activation cascades into the phosphorylation of STATs, leading to their translocation into the nucleus. This intricate sequence of events culminates in the induction of cellular responses, encompassing processes such as proliferation, differentiation, migration, apoptosis, and immune modulation, orchestrated through the activation of various genes. The JAK family encompasses four isoforms, namely JAK1, JAK2, JAK3, and tyrosine kinase inhibitor 2 (TYK2), whereas the STAT family comprises seven distinct members. Different JAK complexes transduce specific cytokine signaling pathways. For instance, the JAK1-JAK3 complex, vital for lymphocyte proliferation and homeostasis, is stimulated by cytokines such as IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, whereas IL-6 signaling is transduced by a combination of JAK1, JAK2, and TYK2 (6,7). Jakinibs, through their pharmacological action, bind to JAKs and interfere

with their phosphorylation, thereby modulating the ensuing cellular responses, as previously elucidated. Notably, each Jakinib exhibits a distinct primary target and selectivity profile. Tofacitinib, baricitinib, ruxolitinib, brepocitinib, and ficitinib are considered non-selective in their actions. In contrast, filgotinib, upadacitinib, and solcitinib demonstrate a selective preference for JAK1, whereas decernotinib specifically targets JAK3. In addition, deucravacitinib exerts selective inhibition of TYK2, and R333 offers topical inhibition of JAK1-3/spleen tyrosine kinase (SYK) (7) (see Figure 1 for a visual representation).

### Preclinical and Clinical Investigations of Jakinibs for SLE

**Tofacitinib:** Tofacitinib, a non-selective TYK that targets the JAK1-JAK3 pathway, has gained approval for the treatment of RA, psoriatic arthritis (PsA), and ulcerative colitis (8). In the context of lupus pathogenesis, tofacitinib has demonstrated its efficacy in reducing proinflammatory cytokines that play a pivotal role in the development of lupus (9,10). This reduction is achieved by the suppression of IFN-dependent JAK-STAT-related genes, as evidenced by the female lupus mouse model (MRL/lpr) that exhibits typical SLE features (11). Moreover, experimental studies have highlighted tofacitinib's potential benefits within the vascular system, attributed to its modulation of the innate and acquired immune systems, along with its positive impact on lipoprotein profiles (11,12). The reduction of antinuclear antibody (ANA), anti-dsDNA titers, and proteinuria has also been observed in these studies (11,13,14). A double-blind phase 1 safety study involving tofacitinib found that its use at a dosage of 5 mg twice daily was well-tolerated and safe among patients with SLE (15). Secondary results from this study suggested a potential association with increased high-density lipoprotein levels and a decrease in arterial stiffening via STAT4, which could contribute to the prevention of early atherosclerosis often seen in SLE (15). Case reports in the literature have outlined the efficacy of tofacitinib in SLE. Notably, its use in a case of RA (SLE complicated with RA) resistant to steroids and methotrexate led to decreased C-reactive protein (CRP) levels in the short term and a reduction in high anti-dsDNA titers and clinical lupus disease activity index in the long term. No side effects were reported during the study (16). In a similar study, tofacitinib at 10 mg daily showed success in managing skin, joint, and kidney involvement in two patients with RA who had not responded to multiple other drugs. It was also suggested as an alternative treatment option as a steroid-sparing agent (17). In a case series involving 10 patients with SLE, the addition of 10 mg/day tofacitinib to their existing immunosuppressive treatment effectively addressed clinical symptoms such as arthritis and rash, although no significant changes were observed in serological parameters (18). Other case



**Figure 1.** Jakinibs and their targets

JAK: Janus kinase, Jakinibs: JAK inhibitors, SYK: Spleen tyrosine kinase, TKY2: Tyrosine kinase 2

reports have illustrated complete remission in an SLE patient with Chillblain lesions resistant to standard treatments (19), decreased cutaneous lupus erythematosus (CLE) disease area and severity index (CLASI) scores in cases of CLE unresponsive to immunosuppressive therapy (20), remission of skin lesions in a patient with refractory bullous SLE (21), and successful treatment of resistant alopecia due to SLE with 10 mg/day tofacitinib for 2 years, all without reported side effects (22). Nevertheless, it is important to interpret these studies cautiously, given their small sample sizes and the limited number of controlled studies. Further data are needed to establish efficacy and safety profiles conclusively (see Table 1 for the clinical studies of Jakinibs).

**Baricitinib:** Baricitinib is a selective, reversible inhibitor of JAK1 and JAK2 (23), and it has obtained Food and Drug Administration (FDA) approval for use in active RA unresponsive to TNF inhibitors and alopecia areata. In a study conducted by Lee et al. (24) using a lupus mouse model (MRL/lpr), the effects of baricitinib on renal involvement in SLE were thoroughly explored. Over an 8-week investigation, baricitinib exhibited its effectiveness in averting renal inflammation by inhibiting abnormal B cell activation and reversing podocyte damage (24). Several publications have explored the clinical efficacy of baricitinib through case reviews. Notably, in a treatment-refractory patient presenting with frontal fibrosing alopecia in conjunction with subacute CLE (SCLE), nearly complete recovery was observed following 6 months of baricitinib treatment (25). Zhan et al. (26) reported the achievement of complete remission in a patient with

Blaschkoid linear lupus erythematosus, an uncommon form of SCLE, through 4 mg daily baricitinib for 8 months. Fornaro et al. (27) obtained remission with an 8-week course of 4 mg baricitinib treatment in a patient who had developed a resistant papulosquamous rash in the context of SLE.

Subsequently, some controlled studies associated with baricitinib have been published. In a multicenter international double-blind, placebo-controlled phase 2 study conducted by Wallace et al. (28), SLE patients presenting with skin and joint involvement were randomized into three groups: 2 mg, 4 mg, and placebo. This 24-week study encompassed 315 patients, with the primary endpoint focusing on improvements in arthritis and rash as assessed by the SLE Disease Activity Index-2000 (SLEDAI-2K) index. The baricitinib 4 mg group outperformed the placebo group in relieving the signs and symptoms of active SLE (28). The study noted one case of deep vein thrombosis and six incidents of serious infections in the 4 mg baricitinib group, with no occurrences of mortality, malignancy, or major adverse cardiovascular events reported in any patient (28). In an analysis of the data from this study conducted by Dörner et al. (29), it was observed that patients with positive anti-dsDNA antibodies at baseline who were treated with 4 mg baricitinib exhibited a rapid, sustained, and significant reduction in antibody titers compared with the placebo group. In the SLE-BRAVE-1 study, a multicenter, double-blind, randomized, placebo-controlled phase 3 investigation, active SLE patients were randomized into three arms: baricitinib 4 mg once daily, baricitinib 2 mg once

daily, and placebo, with a follow-up duration of 52 weeks (30). Among the 760 participants, the baricitinib 4-mg arm achieved the primary endpoint of the SLE Response Index-4 (SRI-4) at week 52. However, the study did not reach statistical significance in secondary endpoints such as glucocorticoid dose reduction and lupus low disease activity, falling short of expectations in terms of efficacy (30). In a 52-week, phase 3 placebo-controlled SLE-BRAVE-II study, which continued these investigations with 775 patients equally allocated to 4 and 2 mg doses of baricitinib and placebo, secondary endpoints such as SRI-4, the primary endpoint, and corticosteroid dose reduction were not attained, failing to support the notion of baricitinib as a prospective treatment for SLE patients (31). In summary, the efficacy of baricitinib in patients with SLE has not been conclusively established in controlled studies.

**Ruxolitinib:** Ruxolitinib, an oral TYK with a notable affinity for JAK1 and JAK2, has obtained FDA approval in various forms (5, 10, 15, 20, and 25 mg) for the treatment of myelofibrosis, hydroxyurea-refractory polycythemia vera, and steroid-refractory graft-versus-host disease (32,33). Preclinical studies have indicated significant improvements in the skin findings of MRL/lpr mice, a well-established animal model of lupus, following the administration of ruxolitinib (34). However, it is important to note that these studies did not show regression in autoantibody levels, lymphadenopathy, or splenomegaly (34).

In another experimental investigation, ruxolitinib was reported to reduce the levels of cytokines such as CXCL10, CXCL9, and MxA, which are implicated in CLE, as observed in cutaneous lupus keratinocyte cultures and a 3D human epidermis model of cutaneous lupus (35). Wenzel et al. (36) demonstrated the efficacy of ruxolitinib in a case of treatment-refractory chilblain lupus and proposed that JAK/STAT inhibition holds promise as an approach for the treatment of cutaneous lesions.

**Brepocitinib:** Brepocitinib is a small-molecule TYK2/JAK1 inhibitor, and topical formulations are currently undergoing phase studies in atopic dermatitis (37). Notably, a Phase IIb study focusing on SLE, initiated in 2019, remains ongoing (38).

**Filgotinib:** Filgotinib, an oral small-molecule TYK with selective JAK1 inhibition, has gained approval in the European Union and Japan for the treatment of DMARD-refractory moderate to severe RA (39). In a Phase II randomized, double-blind, multicenter study conducted by Baker et al. (40), 32 biopsy-diagnosed lupus patients with membranous nephropathy were randomized 1:1 to receive filgotinib and lanraplenib, with a 52-week follow-up period. Despite patient dropouts for various reasons, 9 patients completed the study. The primary endpoint of the study was the regression in the amount of proteinuria at week 16. In the filgotinib arm, a notable average 50% reduction in 24-h urine protein was observed. Although the study sample size was limited, it was suggested that filgotinib may present

**Table 1. Clinical studies conducted on Jakinibs for the treatment of SLE**

Jakinibs	Type of lupus	Study ID, design	Number of patients	Study period	Dose of drug	Primary endpoint
Tofacitinib	SLE	NCT02535689, Phase 1 double blind	30	12 weeks	5 mg twice daily	SLEDAI/2K
Tofacitinib	CLE	NCT03288324, Phase 1b/2 open label	20	72 weeks	5 mg twice daily	CLASI-A
Baricitinib	SLE	Phase 2 controlled	315	24 weeks	2 mg, 4 mg	SLEDAI/2K
Baricitinib	SLE	Phase 2 controlled	315	24 weeks	2 mg, 4 mg	Titer of antidsDNA
Baricitinib	SLE	Phase 3 controlled BRAVE-I	760	52 weeks	2 mg, 4 mg	CLASI-A
Brepocitinib	SLE	Phase 2b double blind	349	52 weeks	15 mg, 30 mg	SRI4
Filgotinib	SLE	Phase 2 double blind	9	52 weeks	200mg	decrease in proteinuria
Filgotinib	CLE	Phase 2b double blind	47	12 weeks	200mg	CLASI-A
Upadacitinib	SLE	Phase 2 controlled	341	48 weeks	30mg	SRI4 10 mg <sup>-</sup> steroid dose
Solcitinib	SLE	Phase 2 controlled	50	12 weeks	50 mg, 100 mg, 200 mg	SLEDAI
Deucravacitinib	SLE	Phase 2 controlled	363	32 weeks	6 mg, 12 mg	SRI4

Jakinibs: JAK inhibitors, SLE: Systemic lupus erythematosus, ID: Identification, CLE: Cutaneous lupus erythematosus, SLEDAI/2K: Systemic lupus erythematosus disease activity index-2000, CLASI-A: Cutaneous lupus erythematosus disease area and severity index, SRI4: SLE response index

a novel treatment option for lupus-related renal involvement (40). Another Phase 2 study, in which patients with moderate to severe CLE were randomized one-to-one with filgotinib, lanraplenib, and placebo, assessed the primary endpoint as a 5-point improvement in the CLASI-A score. The nilotinib arm achieved this target in 69% of patients at week 12 (versus 50% in the placebo group and 56% in the lanraplenib group). No major side effects were reported during the study, indicating that the drug was well tolerated (41).

**Upadacitinib:** Upadacitinib, a JAK1-specific second-generation oral small molecule TYK, is used for treating various inflammatory rheumatism diseases such as RA and PsA (42). However, data regarding the use of upadacitinib in SLE are limited. In a case report, upadacitinib was noted to be effective in managing methotrexate-associated nodulosis, granuloma annulare, and arthritis in a female patient with SLE and Jaccoud arthropathy (43).

**Solcitinib (GSK2586184):** Solcitinib, a selective JAK1 inhibitor originally intended for the treatment of psoriasis and ulcerative colitis (44), faced a setback in a clinical trial intended to investigate its safety, tolerability, efficacy, and pharmacodynamic effects in patients with SLE. Unfortunately, the trial could not be completed because of drug-related drug rash with eosinophilia and systemic symptoms syndrome and elevated liver function tests. Following an analysis of the data from the study, it was determined that the use of this treatment in patients with SLE was not advisable (45,46).

**Deucravacitinib:** Deucravacitinib is an oral, selective TYK2 inhibitor that has received FDA approval for the treatment of moderate to severe plaque psoriasis (47). There are limited data on the use of this drug in SLE, with only one case report and one controlled study available. In the case of CLE resistant to treatments such as hydroxychloroquine, mycophenolate mofetil, and tacrolimus, complete lesion improvement was reported with a 4-month regimen of 6 mg/day deucravacitinib treatment. Notably, no adverse events were observed in this case (48). Additionally, in an international multicenter randomized trial involving 363 patients with active SLE, participants received deucravacitinib at doses of 3 mg and 6 mg twice daily or 12 mg once daily, with active treatment being compared with a placebo arm. The primary endpoint of the study was the SRI-4 response at week 32. The results indicated a higher number of patients achieving an SRI-4 response in the deucravacitinib arms (3 mg twice daily and 6 mg twice daily) than in the placebo group. While more improvements were observed in patients receiving a single daily dose of 12 mg compared with the placebo, this

difference did not reach statistical significance. Importantly, no deaths, opportunistic infections, tuberculosis, or major adverse cardiovascular events were reported among the participants (49).

**R333:** R333 is a topical inhibitor targeting JAK1-3 and SYK that has been assessed in patients with discoid lupus erythematosus. In this study, 54 patients with discoid lupus erythematosus were randomly assigned to the R333 and placebo groups, and the evaluation of lesions was conducted using computerized planimetry at week 4 compared to baseline. This study did not yield significant results in terms of lesion activity and area change (50).

## CONCLUSION

The treatment landscape for SLE remains marked by gaps and unmet needs. A crucial requirement persists for novel therapeutic approaches to effectively address the complexities of this disease. Jakinibs have emerged as a potential treatment option with the capacity to intervene in the pathogenesis of SLE. Their promise in SLE treatment lies in their ability to target the fundamental pathophysiological mechanisms underlying this condition and regulate immune system responses. However, it is imperative to accumulate more comprehensive data regarding the clinical efficacy and safety of this innovative treatment approach. Vital questions, including the identification of SLE patient subgroups that may benefit most from Jakinibs, understanding the potential side effects, long-term effects, and feasibility of combining them with other treatment modalities, demand answers. Nevertheless, the potential of Jakinibs for treating SLE remains a focus of future research. The thorough evaluation of this class of drugs through additional clinical trials and randomized controlled trials holds the potential to enhance the quality of life of patients with SLE and positively influence the disease course. In summary, the quest for new and effective treatment options for SLE continues, with Jakinibs poised to assume a pivotal role in this endeavor.

## Footnotes

### Authorship Contributions

Concept: T.D.Y., Design: T.D.Y., Data Collection or Processing: İ.S., Analysis or Interpretation: İ.S., Literature Search: T.D.Y., İ.S., Writing: T.D.Y., İ.S.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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