JAK inhibitors in dermatology: The promise of a new drug class

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New molecularly targeted therapeutics are changing dermatologic therapy. Janus kinase—signal transducer and activator of transcription (JAK-STAT) is an intracellular signaling pathway upon which many different proinflammatory signaling pathways converge. Numerous inflammatory dermatoses are driven by soluble inflammatory mediators, which rely on JAK-STAT signaling, and inhibition of this pathway using JAK inhibitors might be a useful therapeutic strategy for these diseases. Growing evidence suggests that JAK inhibitors are efficacious in atopic dermatitis, alopecia areata, psoriasis, and vitiligo. Additional evidence suggests that JAK inhibition might be broadly useful in dermatology, with early reports of efficacy in several other conditions. JAK inhibitors can be administered orally or used topically and represent a promising new class of medications. The use of JAK inhibitors in dermatology is reviewed here. (J Am Acad Dermatol 2017;76:736-44.)

Key words: alopecia areata; atopic dermatitis; baricitinib; JAK inhibitor; JAK-STAT; psoriasis; ruxolitinib; tofacitinib; vitiligo.

The Janus kinase—signal transducer and activator of transcription (JAK-STAT) pathway is utilized by cytokines including interleukins (ILs), interferons (IFNs), and other molecules to transmit signals from the cell membrane to the nucleus. Upon engagement of extracellular ligands, intracellular JAK proteins, which associate with type I/II cytokine receptors, become activated and phosphorylate STAT proteins, which dimerize and then translocate into the nucleus to directly regulate gene expression[1,2] (Fig 1). The JAK family of kinases includes JAK1, JAK2, JAK3, and tyrosine kinase 2 (Tyk2). Individual JAKs selectively associate with different receptors, but because only 4 JAKs exist, each member is used by multiple different receptors. The same is true of STATs, of which there are 7 family members (STAT 1, STAT 2, STAT 3, STAT 4, STAT 5a, STAT 5b, and STAT 6).[1,2]

Many inflammatory cytokines and other signaling molecules rely on JAK-STAT signaling, which is indispensable for immune and hematopoietic function. For example, loss-of-function mutations in JAK 3 cause severe combined immunodeficiency syndrome.[3,4] Gain-of-function mutations in JAKs act as oncogenes in lymphoproliferative disorders and hematologic malignancies, including cutaneous

Abbreviations used:

AA:	alopecia areata
AD:	atopic dermatitis
AT:	alopecia totalis
AU:	alopecia universalis
CANDLE:	chronic atypical neutrophilic dermatoses with lipodystrophy and elevated temperature
FDA:	Food and Drug Administration
IFN:	interferon
IL:	interleukin
JAK:	Janus kinase
T_H2:	helper T cell type 2
SALT:	Severity of Alopecia Tool
SAVI:	stimulator of interferon genes—associated vasculopathy with onset in infancy
STAT:	signal transducer and activator of transcription
Tyk2:	tyrosine kinase 2

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T cell lymphoma.[5-7] STAT genes are also essential for proper immune function and loss-of-function mutations in these proteins have been associated with immunodeficiency syndromes, including Job syndrome in the case of STAT 3.[8] Certain JAK-STAT polymorphisms are associated with an increased risk of developing autoimmune diseases.[1] In sporadic autoimmune and autoinflammatory conditions, a variety of disease-causing cytokines rely on JAK-STAT signaling to elicit their pathogenic effect.[1,2] Together these observations have led to the development of JAK inhibitors for the treatment of human disease.[9]

CAPSULE SUMMARY

- Janus kinase—signal transducer and activator of transcription (JAK-STAT) signaling contributes to multiple inflammatory dermatoses.
- Recent studies of JAK inhibitors suggest that they are efficacious for alopecia areata, atopic dermatitis, psoriasis, and vitiligo, and a large number of clinical trials are currently underway.
- JAK inhibitors are likely to have broad applicability in dermatology.

The first generation of JAK inhibitors includes tofacitinib, ruxolitinib, baricitinib, and oclacitinib (Table I). Ruxolitinib is Food and Drug Administration (FDA) approved to treat myelodysplastic disorders. Baricitinib is not yet FDA approved but is in clinical trials for rheumatoid arthritis (RA) (phase 3),[10] psoriasis (phase 2),[11] and atopic dermatitis (phase 2, NCT02576938). The first FDA-approved JAK inhibitor for treatment of an autoimmune disease was tofacitinib, although it was initially studied as an antirejection agent in organ transplantation.[12] Oclacitinib has no FDA-approved indication in humans and is used for treatment of atopic dermatitis (AD) in dogs.[13,14] Second generation JAK inhibitors are in development and will be discussed further below.

In the past 3 years, it has become clear that in addition to psoriasis JAK inhibitors might be useful for other inflammatory dermatologic conditions. Many of the following dermatologically relevant cytokines rely on the JAK-STAT pathway: IFN-α/β; IFN-γ; IL-2 receptor common γ-chain interleukins (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21); IL-5; IL-6; IL-12; IL-13; and IL-23 (Table II). Although other cytokines such as tumor necrosis factor—α, IL-1, and IL-17 do not signal via the JAK-STAT pathway, in some instances JAK inhibitors can indirectly suppress certain cytokines (ie, IL-17) by inhibition of other STAT-dependent cytokines (ie, IL-23) that act upstream.[1,55,56]

To date, JAK inhibitors have shown efficacy in the treatment of dermatologic conditions such as AD, alopecia areata (AA), psoriasis, and vitiligo, among others. Both new, oral JAK inhibitors and topical JAK inhibitors are being developed and studied in these and other dermatologic conditions. Smaller case series and case reports suggest efficacy in dermatomyositis, chronic actinic dermatitis, erythema multiforme, hypereosinophilic syndrome, cutaneous graft-versus-host disease, and lupus, among others.

ATOPIC DERMATITIS

The pathogenesis of AD is complex but in part involves increased helper T cell type 2 (T_H2) immunity driven by JAK-STAT signaling downstream of cytokines, such as IL-4, IL-5, and IL-13.[57] In experimental models, tofacitinib and oclacitinib inhibit IL-4 and IL-13—dependent T_H2 differentiation.[14,55,58] In a mouse model of AD, a topical JAK inhibitor, JTE-053, resulted in decreased IL-4 and IL-13 signaling and improved skin barrier function.[59]

The efficacy of oral tofacitinib was recently reported in 6 consecutive patients with moderate-to-severe AD that previously failed all common treatments, including systemic agents.[31] Tofacitinib 5 mg daily or twice daily led to a 66.6% reduction in the Severity Scoring of AD Index and a 69.9% reduction in pruritus and sleep loss scores.[31] While this study lacked a control group, the improvement achieved by 6 patients who had failed common therapies was suggestive of a positive benefit of tofacitinib.

A recently published randomized, double-blind, placebo-controlled phase 2a trial showed that treatment of 69 adults with mild-to-moderate AD with tofacitinib 2% ointment resulted in an 81.7% reduction in the Eczema Area and Severity Index score at 4 weeks relative to a decrease of 29.9% in the placebo group.[32] Additional clinical trials evaluating both oral and topical JAK inhibitors for AD are underway (NCT02001181, NCT02576938, NCT02780167) and will help to define the efficacy of JAK inhibitors in AD.

ALOPECIA AREATA

The pathogenesis of AA involves hair follicle attack by autoreactive $CD8^+$ T cells.[60] In AA, JAK-STAT dependent cytokines, including IFN-γ and IL-15, drive proliferation and activation of autoreactive T cells,[60] suggesting that JAK inhibition might be an effective treatment. In a mouse model of

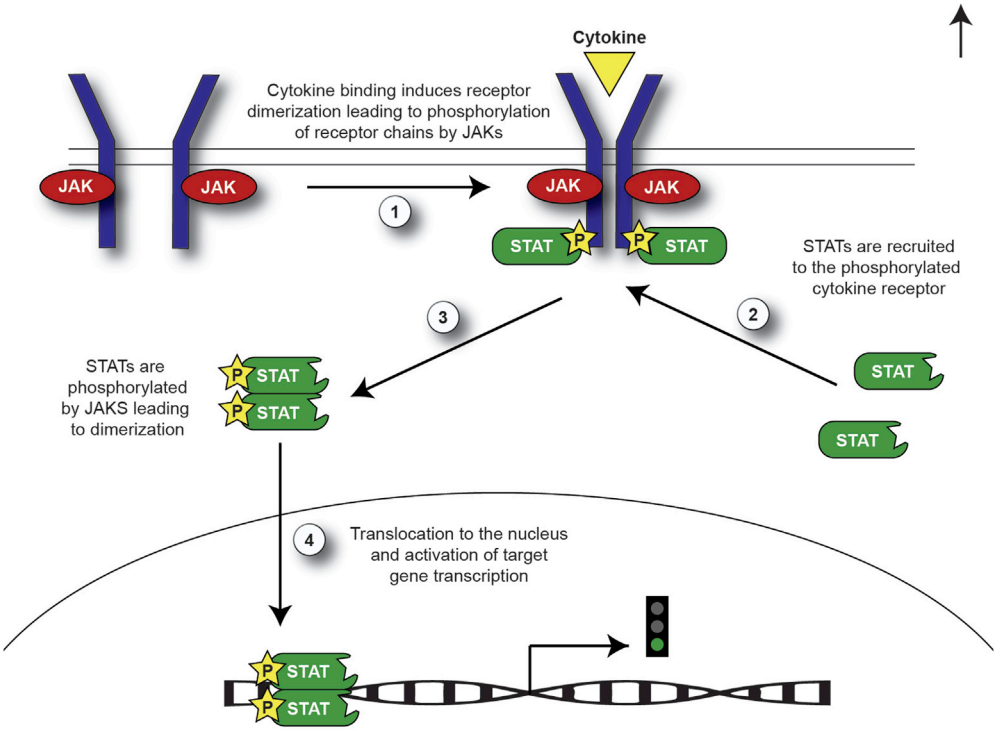

Fig 1. Janus kinase–signal transducer and activator of transcription (JAK-STAT) signaling pathway. JAK inhibitors antagonize JAK protein function and prevent activation of the pathway.

Table I. First generation JAK inhibitors

Drug	Inhibits	FDA-approved indications	FDA-approved dosage
Tofacitinib	JAK1/3 > 2	Rheumatoid arthritis	5 mg, twice daily 11 mg ER, once daily
Ruxolitinib	JAK1/2	Myelofibrosis	5-25 mg, twice daily
		Polycythemia vera	5-25 mg, twice daily
Baricitinib	JAK1/2	None	None
Oclacitinib	JAK1	Canine atopic dermatitis	N/a

ER, Extended release; *FDA*, Food and Drug Administration; *JAK*, Janus kinase; *N/a*, not applicable.

AA, both systemic and topical JAK inhibitors (tofacitinib and ruxolitinib) promoted hair regrowth.[26]

In 2014, a patient with both alopecia universalis (AU) and psoriasis was treated with tofacitinib, and complete regrowth of scalp and body hair, as well as eyelashes and eyebrows, occurred within 8 months.[20] Since then, 2 open-label clinical trials and multiple case series of adolescent and adult patients and case reports have been published (Table II). In one trial, tofacitinib 5 mg twice daily was given to 66 patients with severe AA, alopecia totalis (AT), or AU. After the 3-month treatment period, nearly two-thirds of patients showed some hair regrowth and 32% of patients achieved a >50% improvement in their Severity of Alopecia Tool (SALT) score.[15] In the second study, treatment of 12 patients with moderate-to-severe AA with ruxolitinib 20 mg twice daily for 3-6 months resulted in a marked treatment response in 9 patients, with an average of 92% hair regrowth.[17] Hair loss appears to recur with treatment discontinuation.[15,17]

Recently, 2 retrospective studies showed successful treatment of severe AA, AT, and AU over a period up to 18 months using tofacitinib. In 65 adults with either AT or AU with duration of current episode ≤10 years or severe AA, 77% of patients achieved some hair regrowth, with 58% achieving >50% improvement and 20% achieving >90% improvement in SALT score. Hair regrowth was attenuated in patients with AT and AU with duration >10 years.[18] In a series of adolescents (12-17 years old) with severe AA, AT, and AU, treatment with tofacitinib resulted in a 93% median change in SALT score from baseline after an average of 6.5 months of

Table II. Summary of JAK-inhibitor use in the treatment of dermatologic conditions

Disease	Evidence for oral therapy	Evidence for topical therapy
Alopecia areata	OCT-tofacitinib[15]	CR-ruxolitinib[16]
	OCT-ruxolitinib[17]	
	CS-tofacitinib[18,19]	
	CR-tofacitinib[20-25]	
	CR-ruxolitinib[26-29]	
	CR-baricitinib[30]	
Atopic dermatitis	CS-tofacitinib[31]	RCT-tofacitinib[32]
Chronic actinic dermatitis	CR-tofacitinib[33]	
Chronic mucocutaneous candidiasis	CR-ruxolitinib[29,34]	
Cutaneous T-cell lymphoma	Other[5]	
Dermatomyositis	CR-tofacitinib[35,36]	
	CR-ruxolitinib[37]	
Erythema multiforme	CR-tofacitinib[38]	
Graft-versus-host disease (cutaneous)	CS-ruxolitinib[39]	
Hypereosinophilic syndrome	CS-tofacitinib[40]	
Lupus erythematosus	CR-tofacitinib[41,42]	
	CR-ruxolitinib[43]	
Mastocytosis and mast cell disease	CR-ruxolitinib[44]	
STING vasculopathy	CR-tofacitinib[42]	
	CR-ruxolitinib[45]	
Palmoplantar pustulosis	CR-tofacitinib[46]	
Polyarteritis nodosa	CR-tofacitinib[47]	
Psoriasis	RCT-tofacitinib[48,49]	RCT-tofacitinib[50,51]
	RCT-baricitinib[11]	CS-ruxolitinib[52]
	Others*	
Vitiligo	CR-tofacitinib[53]	CS-ruxolitinib[54]
	CR-ruxolitinib[27]	

Other designates in vitro data on human tumor cells.
CR, Case reports (<5 patients/study); *CS*, case series (≥5 patients/study); *JAK*, Janus kinase; *OCT*, open-label clinical trial; *RCT*, randomized-controlled trial; *STING*, stimulator of interferon genes.
*Multiple earlier studies not included.

treatment.[19] Although this study lacked a control group, spontaneous improvement in patients with long-standing, severe disease is unlikely, so these results are promising.

In 3 patients with AU and nail dystrophy, tofacitinib 5 mg twice daily for 5-6 months resulted in remission of nail dystrophy.[21] The use of oral JAK inhibitors in AA remains an active area of clinical investigation.

As in AD, topical JAK inhibitors are under investigation in AA. In one report, a patient treated with compounded ruxolitinib 0.6% cream applied twice daily for 12 weeks to the eyebrows and scalp led to complete eyebrow regrowth and partial scalp hair regrowth.[16] Clinical trials with topical ruxolitinib (INCB018424) and topical tofacitinib are presently underway in AA (NCT02553330, NCT02812342).

PSORIASIS

JAK-STAT–dependent cytokines IL-12 and IL-23 are fundamental mediators of psoriasis.[61,62] IL-23 stimulates T_H17 cells to produce IL-17, another important pathogenic molecule in psoriasis. Although IL-17 does not rely on JAK-STAT signaling, blockade of upstream IL-23 using JAK inhibitors such as tofacitinib indirectly results in a decrease in IL-17.[55,61] To date, in dermatology, psoriasis has been the most heavily studied indication for JAK inhibitors. JAK inhibitor use in psoriasis has recently been extensively reviewed[62] and will be only briefly reviewed here.

The efficacy of tofacitinib in moderate-to-severe plaque psoriasis was shown in phase 3 randomized controlled trials.[48,49] In one of the studies, the Psoriasis Area Severity Index 75 response to tofacitinib at 12 weeks was 39.5% and 63.6% in the 5 mg twice daily and 10 mg twice daily groups, respectively.[49] Tofacitinib at 10 mg twice daily was determined to be noninferior to etanercept therapy (50 mg subcutaneously twice weekly).[49] Rates of adverse events appeared to be similar with both the 5 mg and 10 mg dosing regimens.[48,49] Comparable results were present in another trial.[48] The FDA has yet to approve tofacitinib for this indication.

Baricitinib, still in clinical trials and not yet FDA approved for any condition, was recently reported to be efficacious in moderate-to-severe plaque psoriasis in a phase 2b trial.[11] In this 12-week dose ranging study, patients treated with 8 mg and 10 mg once daily achieved Psoriasis Area Severity Index 75 responses of 43% and 54%, respectively.[11]

The use of topical JAK inhibitors has been explored in psoriasis. Ruxolitinib (INCB018424) 1.0% and 1.5% creams applied twice daily led to reduction in psoriasis lesion size over 4 weeks.[52] Improvement in psoriasis was also observed with tofacitinib 2% ointment; however, the degree of improvement relative to controls was modest and not always statistically significant.[50,51]

VITILIGO

Vitiligo is mediated by targeted destruction of melanocytes by $CD8^+$ T cells, with IFN-γ playing a central role in disease pathogenesis.[63,64] Because IFN-γ signaling utilizes the JAK-STAT pathway, vitiligo might be susceptible to treatment with JAK inhibitors. For example, treatment of a patient with generalized vitiligo with tofacitinib resulted in near complete repigmentation of affected areas of the face, forearms, and hands over 5 months[53]; however, depigmentation recurred after discontinuing tofacitinib. In another report, a patient who had both vitiligo and AA was treated with ruxolitinib 20 mg twice daily and over 20 weeks experienced significant facial repigmentation; depigmentation recurred after discontinuing ruxolitinib.[27]

A pilot study involving 12 patients with vitiligo is underway investigating the efficacy of ruxolitinib 1.5% cream applied twice daily (NCT02809976). Larger controlled studies will be important for elucidating the role of JAK inhibitors in the treatment of vitiligo.

TOPICAL JAK INHIBITORS

While not commercially available, the use of topical JAK inhibitors has been explored in AD, psoriasis, AA, and vitiligo. Multiple studies are ongoing in this area. The data for topical therapy in each disease are discussed above and summarized in Table II.

SAFETY DATA

Safety data for tofacitinib is derived from large clinical trials in rheumatoid arthritis and psoriasis,[65-68] and data for ruxolitinib are from clinical trials in myelofibrosis and polycythemia vera.[69-71]

The risk of infection and overall mortality in patients treated with tofacitinib is not significantly different from that observed with other targeted immunosuppressive therapies.[65-67] With ruxolitinib, the most common infection was urinary tract infection.[69,71] With both tofacitinib and ruxolitinib, the risk for varicella zoster virus reactivation increases,[69,71,72] but it is usually limited to localized disease. Impaired response to vaccination has been reported with tofacitinib and is theoretically a risk with ruxolitnib, too. Therefore, when possible, immunizations should be performed prior to initiating therapy with JAK inhibitors.[1,73]

Increases in total cholesterol, low-density lipoprotein, and high-density lipoprotein have been reported with tofacitinib and ruxolitinib therapy but are typically mild.[1,68,74,75] Patients treated with JAK inhibitors do not appear to have an increased risk for major adverse cardiac events or stroke.[65,68,76,77]

Cytopenias are another potential adverse effect of JAK inhibitors, primarily JAK2 inhibitors, because signaling through JAK2 is mediated by erythropoietin, thrombopoietin, and granulocyte colony-stimulating factor.[1] Accordingly, cytopenias are more commonly encountered with ruxolitinib than tofacitinib due to its greater ability to inhibit JAK2. In the treatment of bone marrow disorders with ruxolitinib, thrombocytopenia, in particular, can lead to reduced patient doses,[78] but in a study of 12 patients with AA treated with ruxolitinib 20 mg twice daily for up to 6 months, neither this nor other cytopenias were observed.[17] One explanation might be that patients with healthy bone marrows are less prone to cytopenias observed during JAK2 inhibition.

A concern with JAK inhibitors is a theoretical increased risk for malignancy because immunosuppression could dampen antitumor immune surveillance. Initial studies of tofacitinib in renal transplantation showed that ~1% of patients treated with tofacitinib developed post-transplant lymphoproliferative disorder.[79-81] However, in these studies patients were treated with high doses of tofacitinib (10-30 mg twice daily) in combination with other immunosuppressive agents (ie, IL-2 receptor anatagonists, mycophenolate mofetil, and corticosteroids). An increased risk of lymphoproliferative disorders and other cancers has not been apparent when tofacitinib is used to treat inflammatory disorders, such as rheumatoid arthritis and psoriasis[65,68,82,83]; longer term studies, however, will more definitively answer this question. In patients with myelofibrosis and polycythemia vera treated with ruxolitinib, no increased risk for developing a second malignancy has been shown.[84,85]

USE OF JAK INHIBITORS

The FDA-approved dosage for tofacitinib in rheumatoid arthritis is 5 mg twice daily. A new

extended-release formulation (11 mg once daily) is also available. In clinical trials on psoriasis, tofacitinib 10 mg twice daily was more efficacious than 5 mg twice daily and adverse events did not seem to increase with the higher dosage.[48,49] On the basis of the current literature describing treatments for inflammatory skin disorders, 5 mg twice daily is often sufficient but 10 mg twice daily is sometimes required. Dose reduction is required with severe renal impairment, with moderate hepatic impairment, or with the use of medications such as fluconazole and ketoconazole, which inhibit CYP3A4 and CYP2C9.

The FDA-approved dosage of ruxolitinib for myelofibrosis and polycythemia vera ranges from 5 mg to 25 mg twice daily. Twenty milligrams twice daily was used in the open-label clinical trial in AA.[17] Similar to tofacitinib, dose adjustment with ruxolitinib is required in the setting of concomitant CYP3A4 and CYP2C9 inhibitors, as well as with hepatic and renal impairment.

Prior to treatment with tofacitinib or ruxolitinib, serologic screening, including complete blood count, creatinine and hepatic function panel, and fasting lipid panel together with hepatitis B, hepatitis C, and tuberculosis testing is recommended. We also suggest screening for HIV. Subsequently, monitoring complete blood count, creatinine and hepatic function panel, and fasting lipid panel 1 month after treatment and then every 3 months thereafter is recommended. Tuberculosis screening should be performed annually.

CONCLUSIONS AND FUTURE DIRECTIONS

In addition to the conditions already discussed, JAK inhibitors have shown promise in multiple other dermatologic diseases, including dermatomyositis, chronic actinic dermatitis, erythema multiforme, hypereosinophilic syndrome, cutaneous graft-versus-host disease, and lupus, among others (Table II). Preclinical data suggests that JAK inhibition might be a viable strategy to treat multiple other dermatoses, including allergic contact dermatitis[86,87] and interface dermatoses, such as lichen planus,[88-90] B-cell–mediated disorders,[91] pyoderma gangrenosum,[90] chronic cutaneous lupus,[90] and eosinophil related disorders.[92,93] There is a compassionate use protocol for JAK1 and JAK2 inhibition in rare autoinflammatory syndromes including SAVI (stimulator of interferon genes–associated vasculopathy with onset in infancy), CANDLE (chronic atypical neutrophilic dermatoses with lipodystrophy and elevated temperature) syndrome, and juvenile dermatomyositis (NCT01724580).

Presently at least 25 separate clinical trials are underway to evaluate the use of JAK inhibitors in a variety of autoimmune and inflammatory diseases.[1] A new generation of JAK inhibitors, including both pan-JAK inhibitors (JAK1, JAK2, JAK3, and Tyk2) and selective JAK inhibitors (ie, JAK1 only or JAK3 only), are being developed.[2,30,94-100] The advent of JAK inhibitors in dermatology has been met with great interest. This class of medications has the potential to substantially advance the treatment of inflammatory dermatoses.

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