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

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Abstract

New molecularly targeted therapeutics are changing dermatologic therapy. JAK-STAT is an intracellular signaling pathway upon which many different pro-inflammatory 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 may be a useful therapeutic strategy for these diseases. There is growing evidence that JAK inhibitors are efficacious in atopic dermatitis, alopecia areata, psoriasis, and vitiligo. Additional evidence suggests that JAK inhibition may 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.

Keywords

Tofacitinib; ruxolitinib; baricitinib; JAK-STAT; JAK inhibitor; alopecia areata; atopic dermatitis; psoriasis; vitiligo

Introduction

The Janus kinase and signal transducer and activator of transcription (JAK-STAT) pathway is utilized by cytokines including interleukins, 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 to the nucleus to directly regulate gene expression[1,2] (Figure 1). The JAK family of kinases includes JAK1, JAK2, JAK3, and TYK2. Individual JAKs selectively associate with different receptors, but as there are only four JAKs, each member is used by multiple different receptors. The same is true of STATs, of which there are seven family members (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6)[1,2].

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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 JAK3 cause severe combined immunodeficiency syndrome (SCID)[3,4]. Gain-of-function mutations in JAKs act as oncogenes in lymphoproliferative disorders and hematologic malignancies, including cutaneous T cell lymphoma[5–7]. STAT genes are also essential for proper immune function and loss-of-function mutations in these proteins can be associated with immunodeficiency syndromes, including Job's syndrome in the case of STAT3[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 in order 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].

The first generation of JAK inhibitors includes tofacitinib, ruxolitinib, baricitinib, and oclacitinib (Table I). Ruxolitinib is 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 anti-rejection 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 there are other inflammatory dermatologic conditions for which JAK inhibitors might be useful. Many dermatologically relevant cytokines rely on the JAK-STAT pathway and include: 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), and IL-5, IL-6, IL-12, IL-13, and IL-23 (Table II). Although other cytokines such as TNF-α, IL-1, and IL-17 do not signal via the JAK-STAT pathway, in some instances JAK inhibitors can indirectly suppress these cytokines (i.e. IL-17) by inhibition of other STAT-dependent cytokines (i.e. IL-23) that act upstream[1,15,16].

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. Preclinical data suggests that the usefulness of JAK inhibitors may be even broader than these early clinical studies suggest.

Atopic dermatitis

The pathogenesis of AD is complex, but is in part the result of increased Th2 immunity driven by JAK-STAT signaling downstream of cytokines such as IL-4, IL-5, and IL-13[17]. In experimental models, tofacitinib and oclacitinib inhibit IL-4 and IL-13 dependent Th2

differentiation[14,15,18]. 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[19].

The efficacy of oral tofacitinib was recently reported in 6 consecutive patients with moderate-to-severe AD that had failed all common treatments, including systemic agents[20]. Tofacitinib 5mg daily or twice daily led to a 66.6% reduction in the Severity Scoring of AD Index (SCORAD) and a 69.9% reduction in pruritus and sleep loss scores[20]. 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 (EASI) score at 4 weeks, relative to a decrease of 29.9% in the placebo group[21]. 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[22]. In AA, JAK-STAT dependent cytokines including IFN-γ and IL-15 drive proliferation and activation of autoreactive T cells[22], suggesting that JAK inhibition might be an effective treatment. In a mouse model of AA, both systemic and topical JAK inhibitors (tofacitinib and ruxolitinib) promoted hair regrowth[23].

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[24]. Since then, 2 open-label clinical trials have been published in addition to case series of adolescent and adult patients and case reports (Table II). In one trial, tofacitinib 5mg 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[25]. In the second study, treatment of 12 patients with moderate-to-severe AA with ruxolitinib 20mg twice daily for 3–6 months resulted in a marked treatment response in 9 patients, with an average of 92% hair regrowth[26]. Hair loss appears to recur with treatment discontinuation[25,26].

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/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/AU with duration >10 years[27]. 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 treatment[28]. Although these studies lacked a control group,

because there is a low likelihood of spontaneous improvement in patients with long-standing and severe disease, the results are very promising.

In 3 patients with AU and nail dystrophy, tofacitinib 5mg twice daily for 5–6 months resulted in remission of nail dystrophy[29]. 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[30]. 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[31,32]. IL-23 stimulates TH17 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[15,31]. To date, in dermatology, psoriasis has been the most heavily studied indication for JAK inhibitors. JAK inhibitor use in psoriasis has recently been more extensively reviewed[32], but will be briefly reviewed here.

The efficacy of tofacitinib in moderate-to-severe plaque psoriasis was shown in phase 3 randomized controlled trials[33,34]. In one of the studies, the PASI 75 response to tofacitinib at 12 weeks was 39.5% and 63.6% in the 5mg twice daily and 10mg twice daily groups, respectively[34]. Tofacitinib at 10mg twice daily dosing was determined to be non-inferior to etanercept therapy (50mg subcutaneously twice weekly)[34]. Rates of adverse events appeared to be similar in both the 5mg and 10mg dosing regimens[33,34]. Comparable results were present in the other trial[33]. 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 8mg and 10mg once daily achieved PASI 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[35]. 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[36,37].

Vitiligo

Vitiligo is mediated by targeted destruction of melanocytes by CD8 T cells, with IFN-γ playing a central role in disease pathogenesis[38,39]. IFN-γ signaling utilizes the JAK-STAT pathway, and therefore vitiligo may 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[40]; however, depigmentation recurred after discontinuing tofacitinib. In another report, a patient who had both vitiligo and AA was treated with ruxolitinib 20mg twice daily and over 20 weeks experienced significant facial repigmentation; depigmentation recurred after discontinuing ruxolitinib[41].

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 RA and psoriasis[42–45], and data for ruxolitinib are from clinical trials in myelofibrosis and polycythemia vera[46–48].

The risk of infection and overall mortality in patients treated with tofacitinib is not significantly different from that observed with other targeted immunosuppressive therapies[42–44]. With ruxolitinib, the most common infection was urinary tract infection[46,48]. With both tofacitinib and ruxolitinib, there is increased risk of varicella zoster virus reactivation[46,48,49], 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[1,50].

Increases in total cholesterol, LDL cholesterol, and HDL cholesterol have been reported with tofacitinib and ruxolitinib therapy, but are typically mild[1,45,51,52]. Patients treated with JAK inhibitors do not appear to have an increased risk of major adverse cardiac events or stroke[42,45,53,54].

Cytopenias are another potential adverse effect of JAK inhibitors, primarily JAK2 inhibition, because signaling via JAK2 is utilized by erythropoietin, thrombopoietin, and G-CSF[1]. Accordingly, cytopenias are more commonly encountered with ruxolitinib than tofacitinib due to its greater inhibition of JAK2. In the treatment of bone marrow disorders with ruxolitinib, thrombocytopenia, in particular, can be dose limiting[55], but in a study of 12 patients with AA treated with ruxolitinib 20mg twice daily for up to six months, neither this nor other cytopenias were observed[26]. It may be that patients with healthy bone marrows are less vulnerable to the cytopenias observed with JAK2 inhibition.

A concern with JAK inhibitors is a theoretical increased risk of malignancy, because immunosuppression could dampen anti-tumor immune surveillance. Initial studies of

tofacitinib in renal transplantation showed that ~1% of patients treated with tofacitinib developed post-transplant lymphoproliferative disorder[56–58]. However, in these studies patients were treated with higher doses of tofacitinib (10–30mg twice daily) and in combination with other immunosuppressive agents, i.e. IL-2R 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 RA and psoriasis[42,45,59,60]; longer term studies, however, will more definitively answer this question. In patients with myelofibrosis and polycythemia vera treated with ruxolitinib, no increased risk of developing a second malignancy has been shown[61,62].

Use of JAK inhibitors

The FDA approved dose for tofacitinib in RA is 5mg twice daily. A new extended release formulation (11mg once daily) is also available. In psoriasis clinical trials, tofacitinib 10mg twice daily was more efficacious than 5mg twice daily and adverse events did not seem to be different with the higher dose[33,34]. Based on the current literature, for treating inflammatory disorders of the skin, 5mg twice daily is often sufficient, but 10mg twice daily is sometimes required. Dose reduction is required with severe renal impairment, moderate hepatic impairment, or with the use of medications such as fluconazole and ketoconazole, which inhibit CYP3A4 and CYP2C9.

The FDA approved dose of ruxolitinib for myelofibrosis and polycythemia vera ranges from 5mg to 25mg twice daily. 20mg twice daily was used in the open-label clinical trial in AA26. As with tofacitinib, dose adjustment 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 is recommended and includes complete blood count (CBC), creatinine and hepatic function panel (LFTs), and fasting lipid panel together with hepatitis B, hepatitis C, and tuberculosis testing. We also suggest screening for HIV. Subsequently, monitoring CBC, creatinine, LFTs, and fasting lipid panel after 1 month of 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 may be a viable strategy to treat multiple other dermatoses including: allergic contact dermatitis[63,64], inferface dermatoses including lichen planus[65–67], B cell mediated disorders[68], pyoderma gangrenosum[67], chronic cutaneous lupus[67], and eosinophil related disorders[69,70]. There is a compassionate use protocol for JAK1/2 inhibition in rare autoinflammatory syndromes including SAVI (STING 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 (i.e. JAK1 only or JAK3 only), are being developed[2,71–78]. The advent of JAK inhibitors in dermatology has been met with significant excitement. This class of medications has the potential to significantly advance the treatment of inflammatory dermatoses.

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Abbreviations

JAK	Janus kinase
STAT	signal transducer and activator of transcription
TYK2	tyrosine kinase 2
IFN	interferon
IL	interleukin
TNF	tumor necrosis factor
AD	atopic dermatitis
AA	alopecia areata
AU	alopecia universalis
Th2	Type 2 helper T cell
IL-2R	interleukin 2 receptor

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Capsule summary

- JAK-STAT signaling mediates multiple inflammatory dermatoses.
- Recent studies of JAK inhibitors suggest they are efficacious for alopecia areata, atopic dermatitis, psoriasis, and vitiligo, and a large number of trials are currently underway.
- JAK inhibitors are likely to have broad applicability in dermatology.

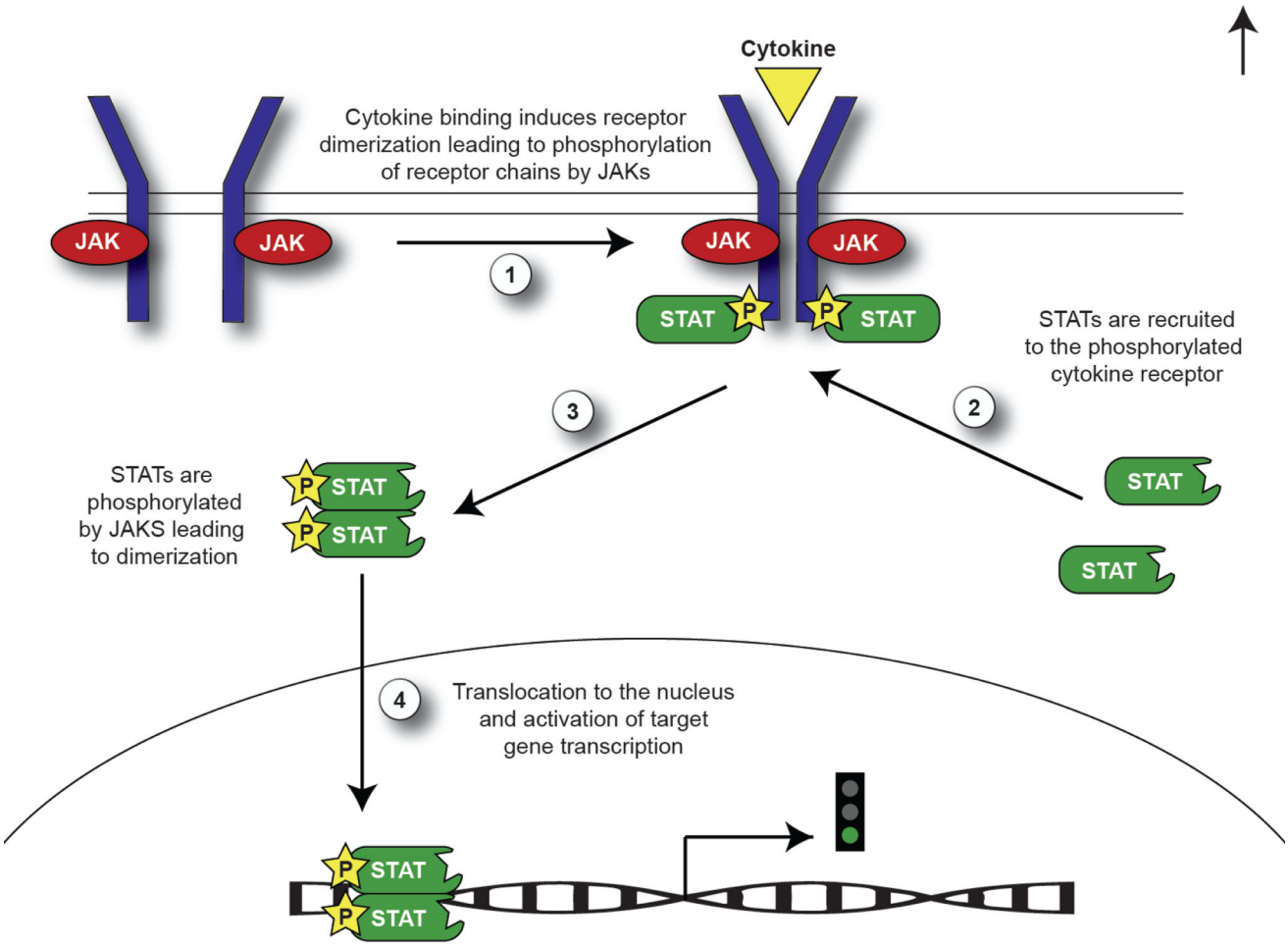

Figure 1.

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 dosing
Tofactinib	JAK1/3 > 2	rheumatoid arthritis	5mg twice daily
			11mg ER * once daily
Ruxolitiniib	JAK1/2	myelofibrosis	5–25mg twice daily
		polycythemia vera	5–25mg twice daily
Baricitinib	JAK1/2	none	none
Oclacitinib	JAK1	(canine atopic dermatitis)	n/a

* Extended release

Table II

Dermatologic conditions for which JAK inhibitors have been utilized in patients.

Disease	Inflammatory mediators	STAT utilized	JAK utilized	Evidence for oral therapy	Evidence for topical therapy
Alopecia areata	IL-15	STAT3/ 5	JAK1/3	OCT-T[30]	CR-R[35]
				OCT-R[31]	
	IFN-γ	STAT1	JAK1, TYK2	CS-T[32,33]	
				CR-T[29,34,86–89]	
				CR-R[28,48,90,91]	
				CR-B[85]	
Atopic dermatitis	IL-4	STAT6	JAK1, JAK3	CS-T[25]	RCT-T[26]
	IL-5	STAT3/5/6	JAK2		
	IL-13	STAT6	JAK1/2/3, TYK2		
Chronic actinic dermatitis	unknown		unknown	CR-T[92]	
Chronic mucocutaneous candidiasis	STAT1 mutation	STAT1	unclear	CR-R[91,93]	
Cutaneous T cell lymphoma	JAK1/3, STAT3/5b mutation	STAT3/5b	JAK1/3	O[5]	
Dermatomyositis	IFN-α/β	STAT1/2/4	JAK1, TYK2	CR-T[94,95]	
				CR-R[96]	
	IL-6	STAT1/3	JAK1/2, TYK2		
	IL-15	STAT3/5	JAK1/3		
Erythema multiforme	IFN-γ	STAT1	JAK1, TYK2	CR-T[97]	
	IL-2	STAT3/5	JAK1/3		
Graft-versus-host disease (cutaneous)	IL-2	STAT3/5	JAK1/3	CS-R[98]	
	IL-6	STAT1/3	JAK1/2, TYK2		
	IL-21	STAT1/3/5	JAK1/3		
	IL-22 (TNF-α, IL-17)	STAT1/3/5	JAK1/2, TYK2		

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Disease	Inflammatory mediators	STAT utilized	JAK utilized	Evidence for oral therapy	Evidence for topical therapy
Hypereosinophilic syndrome	IL-5	STAT3/5/6	JAK2	CS-T**	
	JAK2 mutation (among others)		JAK2		
Lupus erythematosus	IFN-α/β	STAT1/2/4	JAK1, TYK2	CR-T[99,100]	
				CR-R[101]	
	IFN-γ	STAT1	JAK1, TYK2		
	IL-6	STAT1/3	JAK1/2, TYK2		
Mastocytosis / mast cell disease		STAT5		CR-R[102]	
	IL-4	STAT6	JAK1, JAK3		
	IL-5	STAT3/5/6	JAK2		
	IL-13	STAT6	JAK1/2/3, TYK2		
STING vasculopathy	IFN-α/β (STING mutation)	STAT1/2/4	JAK1, TYK2	CR-T[100]	
				CR-R[103]	
Palmoplantar pustulosis	IL-17	Unclear	Unclear	CR-T[104]	
Polyarteritis nodosa	IL-2	STAT3/5	JAK1/3	CR-T[105]	
	IFN-γ (IL-8)	STAT1	JAK1, TYK2		
Psoriasis	IL-12	STAT4	JAK2, TYK2	RCT-T[38,39]	RCT-T[41,42]
				RCT-B[16]	
	IL-23 (TNF-α, IL-17)	STAT3/4	JAK2, TYK2	*others	CS-R[40]
Vitiligo	IFN-γ	STAT1	JAK1, TYK2	CR-T[47]	CS-R**
				CR-R[48]	

CR: case reports (<5 patients/study), CS: case series (≥5 patients/study), OCT: open-label clinical trial, RCT: randomized controlled trial. Other: in vitro data on human tumor cells.

*Multiple earlier studies not included.