JAK-STAT signaling pathway inhibition: a role for treatment of various dermatologic diseases

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Abstract

Cutaneous inflammatory conditions such as psoriasis, atopic dermatitis, alopecia areata, vitiligo, and connective tissue diseases often remain a challenge to treat. Although there is an in-depth understanding of the clinical presentation of these diseases, much less is known regarding the pathophysiology. This has limited the effective treatment options for patients. A more detailed understanding of the pathogenesis of each disease will lead to newer targeted medications with less morbidity. Though there are different pathways involved in these diseases, the Janus Kinase (JAK)-Signal Transducer and Activator of Transcription proteins (STAT) signaling pathway is common to them all. Therefore, this review article endeavors to substantiate the immunopathology and clinical utility of the JAK inhibitors as treatments for different chronic inflammatory diseases of the skin.

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Inflammatory conditions of the skin are common and often challenging to treat, particularly when generalized. Because the pathogenesis of many inflammatory conditions are incompletely understood, patients have relied on systemic immunosuppressant medications that have substantial side effects and are nontargeted. There have been recent advances in revealing the mechanism of action, and it has been found that the Janus Kinase (JAK)-Signal Transducer and Activator of Transcription proteins (STAT) signaling pathway is common to many cutaneous inflammatory diseases. Therefore, JAK-STAT inhibitors provide a possible treatment for diseases, particularly those recalcitrant to standard therapies. The focus of this review article will be on understanding the pathogenesis of cutaneous inflammatory disorders including psoriasis, alopecia areata (AA), vitiligo, atopic dermatitis (AD), and connective tissue diseases. Furthermore, data will be reviewed for the use of JAK inhibitors as potential treatment options in these conditions.

Psoriasis

Psoriasis classically presents with well-demarcated, erythematous plaques with overlying silvery scales. The lesions can be localized to the extensive surfaces of the extremities as well as the scalp but can also cover large body surface areas.[1] In addition to plaque-type psoriasis, other less common variants are inverse psoriasis, pustular psoriasis, and generalized erythroderma. Psoriasis is a hyperproliferative disorder characterized by an overactive immune system, mainly mediated by T-helper type 17 (Th17) cells. Efficacious response to biologic agents that target the Th17 response, such as anti-tumor necrosis factor (TNF)-α, anti-interleukin (IL)-17, and anti-IL-23 antibodies, are commonly used in practice.[2] With further developments being made in the immunological understanding of this inflammatory disease, there is interest in expanding the range of medications that may be offered to patients with psoriasis. With that, clinical trials have been carried out to explore the potential of JAK inhibitors in the treatment of psoriasis. Notably, tofacitinib (Xeljanz; Pfizer, New York, New York) has been analyzed for the treatment of moderate-to-severe chronic plaque psoriasis in multiple phase 3 clinical trials as outlined in the Table. In 2 phase 3 trials for chronic plaque psoriasis evaluating placebo, tofacitinib 5 mg twice a day, and tofacitnib 10 mg twice a day, the Psoriasis Area and Severity Index (PASI) 75 response rate was 6.2%, 39.9%, and 59.2% in the first study and 11.4%, 46%, and 59.6% in the second study.[3]

Tofacitinib has also been widely studied and used clinically in the field of rheumatology; recently, the Food and Drug Administration approved the use of this oral JAK inhibitor in adult patients with active psoriatic arthritis. In a 12-month, double-blind, active-controlled and placebo-controlled phase 3 trial, patients with psoriatic arthritis were randomly assigned to receive either 5-mg tofacitinib orally twice per day, 10-mg tofacitinib orally twice per day, 40-mg adalimumab (anti-TNF-α) by subcutaneous injection once every 2 weeks, placebo with a blind switch to 5-mg tofacitinib at 3 months, or placebo with a blind switch to 10-mg tofacitinib at 3 months.[4] The assay used for efficacy was the American College of Rheumatology 20 (ACR 20), which is defined as having >20% improvement in the number of tender and swollen joints and at least 3 of 5 other important domains at month 3 compared with baseline. ACR 20 response rates at month 3 were 50% and 61% for the 5-mg and 10-mg tofacitinib groups, respectively. This compared with a 33% ACR 20 response rate in the placebo group and 52% in the adalimumab group. In terms of ACR 50 and ACR 70 rates, tofacitinib at the higher dose of 10 mg (40% for ACR 50 and 14% for ACR 70) was found to be superior to that of adalimumab (33% for ACR 50 and 19% for ACR 70).[4]

Atopic dermatitis

The pathophysiology of AD is not fully understood; it is multifaceted, with genetic, environmental, and immunological factors all involved.[5] An elevated Th2 immune response is thought to be the basis for AD disease pathogenesis.[6] Increased levels of Th2 cytokines such as IL-4, IL-5, IL-13, and IL-31 have been noted in AD patients. Dupilumab, a monoclonal antibody that inhibits IL-4 and IL-13 signaling, has recently been approved for adult patients with uncontrolled moderate-to-severe AD. In clinical trials, this drug showed significant reduction in the Eczema Area and Sever-

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ity Index score and better overall outcomes compared with topical corticosteroids.[7,8] Many of the elevated cytokines in cases of AD such as IL-4, IL-5, and IL-13 utilize the JAK-STAT signaling pathway as a means to propagate the Th2 immune response and disease pathogenesis. Therefore, JAK inhibitors have been proposed and are currently being studied as an additional treatment option for AD. In experimental mouse model studies, tofacinitib has been shown to block the differentiation of Th2 cells—an IL-4- and IL-13-dependent process.[9,10]

Case series reports and a phase 2a randomized trial have been

TABLE. Use of JAK inhibitors in the treatment of various dermatologic diseases

Disease/Study Name	Study Type	Patients (N)	Drug/Dosage Used	Outcome
Cutaneous Lupus Erythematosus				
Wenzel et al, 2016[46]	Case report	1	Ruxolitinib: 2 × 20 mg/d	Remission of all lesions within 4 months
ES Chan et al, 2015[33]	Lupus mouse model	-	Tofacitinib	Significant improvement in disease activity; nephritis, skin inflammation, and autoantibody production.
Furumoto et al, 2016[35]	Lupus mouse model	-	Ruxolitinib (oral gavage)	Decreased development of severe skin lesions. At week 4, treated group had significantly reduced lesion severity scores compared with placebo group. Significant reduction in epidermal hyperplasia and inflammatory infiltrate in treated group.
Dermatomyositis				
Kurtzman et al, 2016[47]	Case report	3	Tofacitinib: 10 mg PO and 5 mg PO	All 3 patients showed reduction in CDASI score with clinical response seen after 4 weeks. Patients reported improvement in pruritus, with less fatigue and more strength.
Hornung et al, 2014[48]	Case report	1	Ruxolitinib: 5 mg → 15 mg → 10 mg BID	Thirty-point reduction in CDASI score. Patient regained muscle strength and body weight and skin lesions completely resolved. Patient was able to walk short distances and climb stairs independently at 12-month F/U. Patient remains in remission on ruxolitinib as monotherapy.
Paik JJ, Christopher-Stine L, 2016[49]	Case report	1	Tofacitinib: 5 mg PO BID + 10 mg → 5-mg prednisone PO	Overall improvement in skin, joints, and muscle strength. Within 2 months, improvements in: inflammatory arthritis; Gottron papules, shawl and V-neck sign, and muscle strength. Within 6 months, prednisone tapered off and maintained only on tofacitinib.
Vitiligo				
Rothstein et al, 2017[23]	OCT	9	Ruxolitinib: 1.5% topical cream BID	Seventy-six percent improvement in facial VASI scores at week 20 in 4 patients with significant facial involvement at baseline. 23% improvement in VASI scores in all enrolled patients at week 20. Three out of 8 patients responded on body surfaces. One out of 8 patients responded on acral surfaces.
Craiglow BG, King BA, 2015[21]	Case report	1	Tofacitinib: 5 mg QAD PO → 5 mg/d PO after 3 weeks	After 2 months, partial repigmentation of the face and upper extremities. After 5 months, repigmentation of the forehead and hands nearly complete. Only about 5% total BSA involvement after 5 months. No adverse effects were reported experienced by the patient.
Harris et al, 2016[22]	Case report	1	Ruxolitinib: 2 × 20 mg/d PO	After 12 weeks, noted appearance of pigmented macules, and at week 20, there was large repigmentation of his face and other areas (51% facial pigmentation versus 0.8% at baseline). Twelve weeks after discontinuing ruxolitinib, much of the regained pigment regressed.
Liu et al, 2017[25]	Retrospective case series	10	Tofacitinib	5 patients achieved re-pigmentation at sites of either sunlight exposure or low-dose narrowband ultraviolet B phototherapy. Suction blister sampling showed inhibited autoimmune response to treatment in both responding and non-responding lesions. Concluded that JAK inhibitors provide suppression of overactive T-cell activity and light is required for melanocyte regeneration.

ABBREVIATIONS: AA, alopecia areata; ACR 20, American College of Rheumatology 20; AD, atopic dermatitis; BID, twice daily; BIW, twice weekly; BSA, body surface area; CDASI, Cutaneous Dermatomyositis Disease Area and Severity Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; F/U, follow-up; HRQoL, Health-Related Quality of Life; ISI, Insomnia Severity Index; JAK, Janus Kinase; OCT, ; OPT, oral treatment for psoriasis; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PO, by mouth; PtGA, patient global assessment; SAE, serious adverse event; SALT, Severity of Alopecia Tool; SC, subcutaneous; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroid; VASI, Vitiligo Area Scoring Index.

completed in which both topical tofacitinib (2% cream) and oral tofacitinib (5 mg twice daily and once daily) showed favorable results (Table). Additional clinical trials—in which the JAK 1/2 inhibitor baricitinib (Oluminant; Incyte, Wilmington, Delaware and Eli Lilly, Indianapolis, Indiana), the JAK 1 inhibitor upadacitinib (ABT-494; AbbVie, Lake Bluff, Illinois), and the JAK 1 inhibitor Pf-04965842 are being studied in patients with moderate-to-severe AD (NCT02576938, NCT02925117, and NCT02780167)—are ongoing.[11-13] A specific and noteworthy finding in clinical trials is that JAK inhibitors exhibit potent anti-itch activity.[5,6,14]

TABLE. Use of JAK inhibitors in the treatment of various dermatologic diseases (continued)

Disease/Study Name	Study Type	Patients (N)	Drug/Dosage Used	Outcome
Alopecia Areata				
Craiglow et al, 2015[51]	Case report	1	Ruxolitinib (topical) 0.6% cream BID/12 weeks	After 12 weeks of treatment: complete regrowth of eyebrows with 10% regrowth of scalp hair.
Jabbari et al, 2016[52]	Case report	1	Tofacitinib (oral) 5 mg BID/4 months	Patchy regrowth noted at month 1. 62.5% and 94% of scalp hair regrowth noted at month 2 and 3, respectively. Significant regrowth of eyebrows and eyelashes noted. Scalp hair regrowth nearly complete at month 4. After 4 weeks of treatment, serum and lesional inflammatory markers were decreased.
Anzengruber et al, 2016[53]	Case report	1	Tofacitinib (oral) 5 mg BID/4 months	Scalp remained unchanged at month 2, but after 3 months, growth of short terminal pigmented hair was detected. Relapse with complete alopecia resulted after another month. Note: methotrexate (15 mg/wk) also used in this patient.
Mrowietz et al, 2016[54]	Case report	1	Tofacitinib (oral) 15 mg/d for 6 weeks →10 mg/d for 9 months	After 4 weeks, significant hair regrowth on scalp. Pain and swelling of dactylitis gone. With cont. treatment, hair regrowth seen on all body sites except eyebrows and eyelashes.
Pieri et al, 2015[55]	Case report	1	Ruxolitinib (oral) 15 mg BID/71 months	After 10 months of treatment, presented with improvement of alopecia with significant hair regrowth of almost complete recovery. Sustained response at 50+ months.
Jabbari et al, 2015[56]	Case report	1	Baricitinib (oral) 7 mg/d for 6 months → 7 mg + 4 mg/d	Soon after treatment, significant improvement in AA. After 3 months of treatment, regression to only a single patch of hair loss on occipital scalp.
Craiglow and King, 2014[57]	Case report	1	Tofacitinib (oral) 5 mg BID for 2 months → 10 mg + 5 mg/d for 8 months	After 2 months, partial hair regrowth on scalp and face, and some improvement in psoriasis seen. After 3 months, complete scalp hair regrowth along with significant regrowth of eyebrows/eyelashes along with facial, axillary, and pubic hair. After 8 months, full regrowth of hair at all body sites except arms and legs.
Harris et al, 2016[23]	Case report	1	Ruxolitinib (oral) 20 mg BID	After 4 weeks of treatment, some hair regrowth on frontoparietal scalp noted. After 12 weeks, significant improvement (85% scalp hair versus 63% at baseline). Hair regrowth maintained 12 weeks after discontinuing treatment.
Gupta et al, 2016[58]	Case report	2	Tofacitinib (oral) 5 mg BID for 8 months	Patient 1: significant beard regrowth after 3 months of treatment. By 6 months, hair regrowth noted on all body areas. By 8 months of treatment, scalp hair continued to grow longer and thicker. Eyebrows and eyelashes were seen. Patient 2: noticeable scalp regrowth seen as well as eyelash, eyebrow, and beard regrowth by 4 months. By 8 months, axillary hair regrowth and isolated leg hair noted.
Dhayalan and King, 2015[59]	Case report	3	Tofacitinib (oral) 5 mg/d BID or 10 mg + 5 mg/d for 5-6 months	2 out of 3 of the patients experienced hair growth. All patients showed remission of dystrophic nail changes associated with discomfort or pain after 5-6 months of treatment.

ABBREVIATIONS: AA, alopecia areata; ACR 20, American College of Rheumatology 20; AD, atopic dermatitis; BID, twice daily; BIW, twice weekly; BSA, body surface area; CDASI, Cutaneous Dermatomyositis Disease Area and Severity Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; F/U, follow-up; HRQoL, Health-Related Quality of Life; ISI, Insomnia Severity Index; JAK, Janus Kinase; OCT, ; OPT, oral treatment for psoriasis; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PO, by mouth; PtGA, patient global assessment; SAE, serious adverse event; SALT, Severity of Alopecia Tool; SC, subcutaneous; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroid; VASI, Vitiligo Area Scoring Index.

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Disease/Study Name	Study Type	Patients (N)	Drug/Dosage Used	Outcome
Alopecia Areata				
Erduaran, Adisen and Aksakal, 2017[60]	Case report	1	Tofacitinib (oral) 5 mg BID After 2 months, increase to 10 mg at morning and 5 mg at night.	Initial baseline SALT score for this 23-year-old patient was 100. By month 1 of tx: very fine tiny hair observed. By month 2: partial hair regrowth seen on scalp and eyebrows (SALT = 52). By 6 months, complete hair regrowth throughout entire body with a SALT score of 0. Tofacitinib was tolerated well without any significant side effects.
Xing et al, 2014[61]	Open-label pilot study	3	Ruxolitinib (oral) 20 mg BID for 3-6 months	All patients responded to treatment with near-complete hair regrowth within 5 months of treatment.
Jabbari et al, 2018[62]	Open-label pilot study	12	Toficitinib initial dose 5 mg BID escalated to 10 mg BID	8 out of 12 patients demonstrated >50% hair regrowth 3 patients demonstrated <50% hair regrowth 1 patient demonstrated no regrowth Tofacitinib effective in achieving global overall improvement in SALT score at end of treatment for 11 of 12 patients (average decrease from 81.3% to 40.8%). Patients with either patch-type AA, or AT or AU had on average similar percentage of hair regrowth.
Mackay-Wiggan et al, 2016[63]	Open-label clinical Trial	12	Ruxolitinib (oral) 20 mg BID for 3-6 months	9 out of 12 patients (75%) showed significant response to treatment with an avg. hair regrowth of 92% at the end of treatment.
Craiglow et al, 2016[64]	Retrospective case series	13	Tofacitinib 5 mg BID or 10 mg + 5 mg/d for 2-16 months	10 patients experienced hair regrowth, 1 of whom relapsed and was considered a non-responder. 3 patients experienced minimal hair regrowth. For all patients, median % change in SALT score was 93%. Among responders, median % change in SALT score was 100%.
Liu et al, 2016[65]	Retrospective case series	90	Tofacitinib (oral) 5 mg BID for 4-18 months	77% of patients achieved clinical response of which 58% achieved intermediate (51%-90% SALT score change) or complete response (>90% SALT score change) over 4-18 months. AA patients had better outcomes than AT or AU patients.
Kennedy et al, 2016[66]	2-center open-label single-arm clinical trial	66	Tofacitinib (oral) 5 mg BID for 3 months	32% of the 66 treated subjects experienced 50% or greater improvement in SALT score. AA and ophiasis subjects responded better to treatment than those with AT and AU. Found tofacitinib to be safe and effect for severe AA, yet drug discontinuation resulted in disease relapse within 8.5 weeks.
Park et al, 2017[67]	Retrospective case series	32	Tofacitinib (oral) multiple dose analysis	24 patients (75%) exhibited >5% hair regrowth: 6 with 5%-50% regrowth—7 months, 1,960 mg total 9 with 50%-90% regrowth—9 months, 1,820 mg total 9 with >90% regrowth—10 months, 2,240 mg total 18 patients achieved SALT50 at a median of 3 months tx and 9 patients acquired SALT90 at median of 6 months tx at 10 mg/d. Tofacitinib monotherapy was effective and well tolerated in Korean patients with moderate-to-severe and refractory AA.
Ibrahim et al, 2017[68]	Case series	13	Tofacitinib (oral) 5 mg BID dose increased by 5 mg/mo as allowable by insurance coverage and until treating physician noticed signs of hair regrowth.	Mean pretreatment SALT score was 92.7%, with 2 patients having AT and 7 patients having AU. Re-growth rate was calculated to be a mean (SD) of 44.3% and a median (range) of 50.5%. 7 patients (53.8%) achieved a regrowth of at least 50%. Response time from starting treatment ranged from 1 to 9 months.

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Disease/Study Name	Study Type	Patients (N)	Drug/Dosage Used	Outcome
Atopic Dermatitis				
Levy et al, 2015[6]	Case series	6	Tofacitinib (oral) 5 mg BID (5 patients), 5 mg/d (1 patient)	In all 6 patients, there was decreased BSA of dermatitis with improvement in erythema, edema/papulation, excoriation and lichenification. All patients reported less pruritus and decreased sleep loss. Composite SCORAD index decreased (54.8% reduction at 4-14 weeks and 66.6% reduction at 8-29 weeks on avg.) for all patients and maintained at F/U. Drop in pruritus and sleep loss score was 69.9% and 71.2% (week 4-14)/76.3% and 100% (week 8-29), respectively.
Bissonnette et al, 2016[5]	Phase 2a randomized trial	69	Tofacitinib (topical) 2% tofacitinib BID or vehicle for 4 weeks	EASI score % change from baseline at week 4 for treatment group was –81.7% versus –29.9% for vehicle group. Treatment group showed significant improvements versus vehicle across all efficacy endpoints and for pruritus at week 4. Significant improvements in EASI, PGA, and BSA seen by week 1; improvements in pruritus by day 2.
Guttman-Yassky, et al, 2018[15]	Phase 2 parallel, double-blind placebo-controlled multiple-dose trial	124	Prerandomization (4 weeks): TCS randomization: Once-daily placebo, baricitinib 2 mg or baricitinib 4 mg for 16 weeks	61% of patients who receiving baricitinib 4 mg versus. 37% of patients who received placebo achieved EASI-50 at 16 weeks. Proportion of baricitinib 2- and 4-mg patients achieving EASI-50 compared to placebo was significant as early as week 4. Baricitinib treatment also improved pruritus and sleep loss. Baricitinib used with TCS reduced inflammation and pruritus in patients with moderate-to-severe AD.

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Alopecia areata

Alopecia areata (AA) presents with patches of hair loss on the scalp. Mouse model studies have shed light on the mechanism. Overall, AA is considered a Th1-mediated disease with an immune response consisting mainly of autoreactive cluster of differentiation (CD)8+ T cells.[15] Biopsies of lesioned skin areas have revealed high expression of interferon (IFN)-γ and IFN-γ-induced chemokines—chemokine C-X-C ligand 9 (CXCL9) and CXCL10. IFN-γ is responsible for exposing hair follicles to autoreactive T cells via expression of Major Histocompatibility Complex class I molecules. Additionally, IFN-γ further amplifies the adaptive immune response through chemokine expression, recruiting more T cells. Cytotoxic CD8+ T cells are the ultimate effector cells, which accumulate around the hair bulb and elicit targeted destruction of anagen hair follicles.[15]

Due to the elevation of IFN-γ signaling, the presence of cytotoxic T cells, and presence of various cytokines related to the Th1-mediated immune response, it is likely that targeting the JAK-STAT pathway has therapeutic potential. The use of JAK inhibitors in treating AA has been reported with positive outcomes in various case reports, case series, and open-label clinical trials (Table). Of note, a randomized controlled trial (NCT02553330) evaluating topical ruxolitinib cream (Jakafi; Incyte, Wilmington, Delaware) for moderate-to-severe AA did not reach its primary endpoint and was terminated from further study likely due to lack of penetration of the topical preparation.[16] Clinical trials investigating the efficacy of oral JAK inhibitors in treating moderate-to-severe AA (NCT02299297) are ongoing.[17] If patients discontinue the JAK inhibitor, the hair growth is rapidly lost.

Vitiligo

Vitiligo is an autoimmune disease in which there is a destruction of melanocytes, ultimately causing skin disfiguration and depigmentation.[18] Both males and females are equally affected, and the initial onset of the disease is often a result of emotional stress, illness, or skin trauma such as sunburn. In terms of the disease pathogenesis, CD8+ T cells play a central role in the destruction of melanocytes.[19] Localization of patchy infiltrates of T cells near lesioned melanocytes as well as higher levels of melanocyte-specific CD8+ T cells in the blood of vitiligo patients compared with healthy controls substantiates this claim.

Melanocytes reside at a distance from epidermal blood vessels; therefore, chemokine signaling mechanisms are needed to recruit and promote circulating CD8+ T cells to the peripheral tissue.[15] IFN-γ and IFN-γ-induced chemokines (CXCL9 and CXCL10) are essential in driving this process.[19] IFN-γ binds to the IFN-γ receptor, which activates JAKs, ultimately causing phosphorylation of the transcription factor STAT-1. Once phosphorylated, STAT-1 homodimerizes and translocates into the nucleus, where IFN-γ-induced genes (CXCL9 and CXCL10) are transcribed. These chemokines act as ligands and bind to CD8+ T cells, which then migrate to the skin, where they kill melanocytes. CXCL10 in particular has been found to be elevated in the serum of vitiligo patients compared with healthy controls. Moreover, CXCL10 levels are associated with disease activity and are significantly decreased after successful treatment.[20]

Clinical application of this knowledge has been demonstrated through the use of JAK inhibitors in treating patients with vitiligo.

There are 2 case reports of oral JAK inhibitors successfully repigmenting patients with vitiligo.[21,22]

In addition, an open-label site-initiated trial was completed utilizing 1.5% topical ruxolitinib cream in 12 patients with a minimum of 1% vitiligo-affected body surface area.[23] The primary endpoint was percent improvement in Vitiligo Area Scoring Index from baseline to week 20. Positive results, particularly in facial vitiligo, in this proof-of-concept study led to the initiation of a phase 2 multicenter, randomized, double-blind, dose-ranging clinical trial. Some evidence that combining ambient light or phototherapy with JAK inhibitors may act synergistically and enhance the clinical response has been presented.[24,25] Additional clinical trials are ongoing and are recruiting patients with the purpose of examining the efficacy, safety, and tolerability of INCB018424 cream in cases of vitiligo (NCT03099304).[26]

Discoid lupus erythematosus

The pathophysiology of discoid lupus erythematosus (DLE) is complex, with various components related to immunomodulatory and inflammatory pathways. Lupus mouse models have suggested that IFNs play a major role in disease pathogenesis of cutaneous lupus. The specific result of IFN-binding receptor is tyrosine phosphorylation and subsequent phosphorylation of the JAK-STAT pathway.[27,28] The 2 main classes of IFNs are type I (IFN-α and IFN-β) and II (IFN-γ), and dysregulation of these signaling molecules plays a key

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Disease/Study Name	Study Type	Patients (N)	Drug/Dosage Used	Outcome
Psoriasis				
Bachelez et al, 2015[69]	Phase 3 randomized noninferiority trial	1,106	Group 1: Tofacitinib 5 mg BID Group 2: Tofacitinib 10 mg BID Group 3: 50 mg etanercept SC injection BIW Group 4: Placebo (matched dosing schedule)	Patients with moderate-to-severe plaque psoriasis, 10 mg BID dose of tofacitinib was noninferior to etanercept 50 mg BIW and superior to placebo. 5 mg BID tofacitinib dose did not show noninferiority to entanercept 50 mg BIW AE's over 12 weeks were similar for tofacitinib and entanercept. Concluded future potential of tofacitinib as safe and efficacious treatment for patients with moderate-to-severe plaque psoriasis.
Feldman et al, 2016[70]	2 Phase 3 randomized control trials OPT Trial Pivotal 1 & OPT 2	901 (OPT1) 960 (OPT2)	Randomized 2:2:1 to receive 5 mg tofacitinib, 10 mg tofacitinib or placebo BID After week 16, all placebo treated patients were re-randomized to tofacitinib.	Tofacitinib improved pruritus and health-related quality of life in patients with moderate-to-severe psoriasis over the course of 52 weeks as measured by DLQI, HRQoL, ISI. Greater proportion of patients achieved PtGAk response with tofacitinib 5 and 10 mg BID versus placebo at week 16 (OPT 1: 28.1% and 44.7% all $P < .0001$); PtGA response was maintained in the majority of patients through week 52. By week 16, PtGA and PGA ratings were highly correlated ($P < .0001$).
Asahina et al., 2016[3]	Phase 3 randomized, double-blind clinical trial	20	Week BL-16 (double blind): Tofacitinib 10 mg BID or 5 mg BID Week 16-20 (open label): 10 mg BID Week 20-52 (open label): 10 mg BID or 5 mg BID	Primary end-point (Week 16): 62.8% and 72.8% of patients achieved PASI 75 with tofacitinib 5 and 10 mg BID 67.4% and 68.2% achieved PGA responses. All patients with psoriatic arthritis achieved ACR 20. Responses continued through Week 52. Both doses of tofacitinib demonstrated efficacy in patients with moderate-to-severe plaque psoriasis and/or psoriatic arthritis through 52 weeks. Safety profile consistent with related studies: AE's: 83% of patients SAE's: 4 patients Serious infections (herpes zoster): 3 patients
Scleroderma				
Deverapalli and Rosmarin, 2018[43]	Case report	1	Tofacitinib 5 mg BID	Within 2 weeks, patient with systemic sclerosis noticed improved range of mobility of shoulder joints, decreasing tightening of skin over hands, healing of digital ulcers. Re-pigmentation of affected areas of face after several weeks occurred. No relevant side effects were experienced by the patient.

ABBREVIATIONS: AA, alopecia areata; ACR 20, American College of Rheumatology 20; AD, atopic dermatitis; BID, twice daily; BIW, twice weekly; BSA, body surface area; CDASI, Cutaneous Dermatomyositis Disease Area and Severity Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; F/U, follow-up; HRQoL, Health-Related Quality of Life; ISI, Insomnia Severity Index; JAK, Janus Kinase; OCT, ; OPT, oral treatment for psoriasis; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PO, by mouth; PtGA, patient global assessment; SAE, serious adverse event; SALT, Severity of Alopecia Tool; SC, subcutaneous; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroid; VASI, Vitiligo Area Scoring Index.

role in the pathology of systemic lupus erythematosus (SLE).[27,28] It has also been found that elevated levels of type I and II IFNs are correlated with disease severity in cutaneous forms of lupus.[28,29] This implies that JAK inhibitors may play a significant role in controlling the amplified signaling and overactive inflammatory pathways occurring in the skin of patients with DLE.

In addition to IFNs, various other signaling molecules and immune cells seem to play a role in the activation of the JAK-STAT pathway. Specifically, plasmacytoid dendritic cells (pDCs) are a type of immune cell that releases type I IFN (IFN-α) usually in response to a viral infection.[30] In patients with DLE, however, it has been proposed that sun exposure leads to excessive production and release of TNF-α and IL-1 from keratinocytes, which can also activate pDCs to release excessive amounts of IFN-α.[31] This particular IFN then binds receptors on Th1 cells, which causes the release of IFN-γ—the major initiator and activator of the JAK-STAT pathway.[32] As mentioned above, the end result of activating this inflammatory signaling cascade is gene transcription followed by translation of proteins. Of note are CXCL9 and CXCL10, both of which have been found to be elevated in cell cultures of cutaneous lupus models.[33] It has been shown that chemokine C-X-C receptor 3 and its ligands are responsible for particularly recruiting Th1 cells and eliciting a type

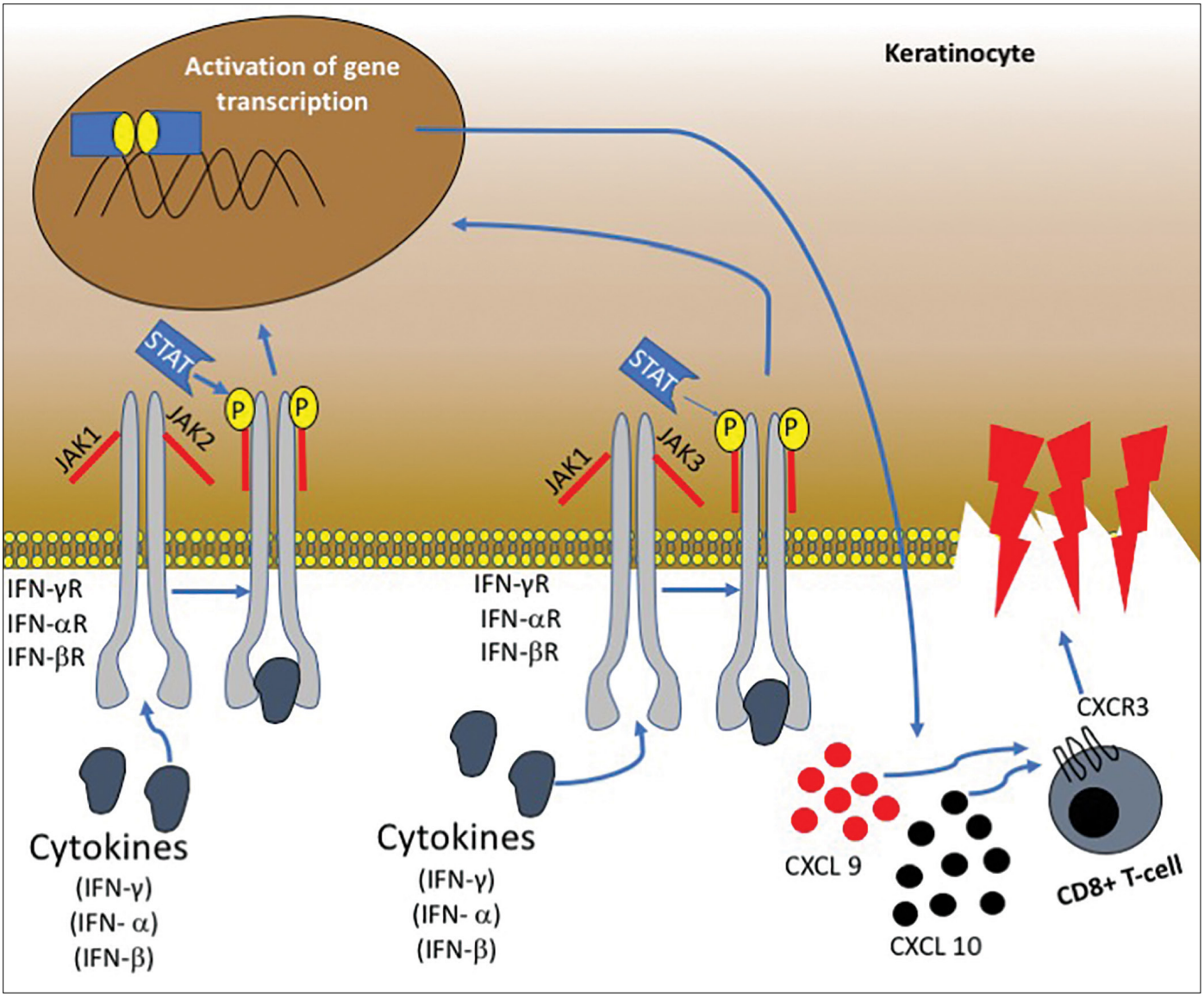

FIGURE 1. JAK-STAT signaling pathway in the pathophysiology in various cutaneous dermatologic conditions. The JAK-STAT pathway is a major pathway involved in the pathophysiology of various conditions such as psoriasis, atopic dermatitis, vitiligo, alopecia areata, and connective tissue disorders. Downstream signaling cascades post cytokine binding to cell membrane receptors result in the transcription and translation of pro-inflammatory cytokines and proteins such as CXCL9 and CXCL10. The ultimate result is destruction of different cell types within the skin through: autoimmune T-cell attack, leukocyte recruitment, complement deposition, and autoantibodies.
ABBREVIATIONS: CXCL, chemokine C-X-C ligand; IFN, interferon; JAK, Janus Kinase; STAT, Signal Transducer and Activator of Transcription.

I inflammatory immune response.[34] In cell cultures treated with ruxolitinib, there was a statistically significant decrease in the expression of these chemokines (CXCL9: $P < .001$; CXCL10: $P < .005$), which demonstrates this drug's ability to decrease the production of chemotactic signals for T cells.[33]

Current evidence in the literature based on mouse models of cutaneous lupus suggests that JAK inhibitors such as ruxolitinib (Jakafi; Incyte, Wilmington, Delaware) and tofacitinib (Xeljanz; Pfizer, New York, New York) can lead to improvements in overall disease activity and specific histological findings such as reduced epidermal hyperplasia and inflammatory infiltrate.[33,35] Although there are few reported data on the outcomes of the use of JAK inhibitors in DLE patients, one case report noted that remission of all cutaneous lesions in a patient with chilblain lupus erythematosus was seen after 4 months of oral ruxolitinib administered at a dose of 20 mg twice daily (Table). Currently, phase 2 clinical trials are being conducted to test the efficacy and safety of JAK inhibitors such as baricitinib for SLE patients and oral tofacitinib for DLE and SLE patients.[36,37] Results of these clinical trials and future ones to follow are needed to better appreciate and determine the degree of efficacy associated with the use of JAK inhibitors in this dermatologic condition.

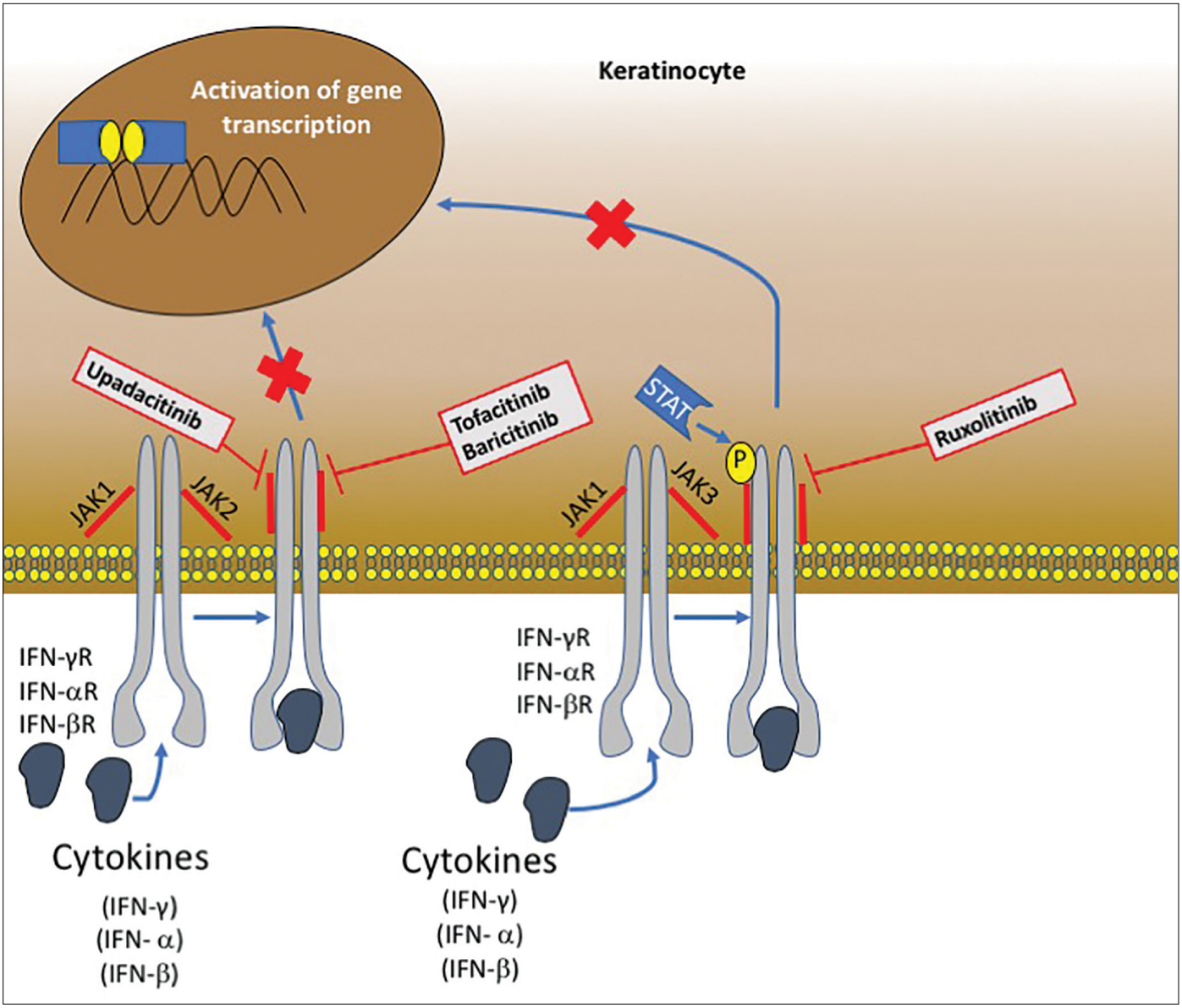

FIGURE 2. Mechanism of action for JAK inhibitors in treatment of various cutaneous dermatologic conditions. JAK inhibitors such as ruxoltinib, tofacitinib, upadacitinib, and baricitinib all target the JAK-STAT signaling pathway and prevent the phosphorylation and subsequent translocation of STAT proteins into the nucleus. Therefore, there is suppression of the production of downstream inflammatory cytokines and proteins, ultimately blocking destruction of skin cells.

ABBREVIATIONS: IFN, interferon; JAK, Janus Kinase; STAT, Signal Transducer and Activator of Transcription.

Dermatomyositis

Similar to the pathophysiology of DLE, the cutaneous manifestation of dermatomyositis (DM) is thought to be largely mediated by the up-regulation of IFNs and IFN-inducible genes.[38] It is thought that via the JAK-STAT signaling pathway, these inflammatory factors result in inflammation, complement activation, and epidermal activation and differentiation.[39]

Biopsies taken from skin lesions of patients with DM have revealed that overactivation of pDCs correlates with elevated levels of type I IFNs.[39,40] These type I IFNs then go on to bind JAK receptors located on most human cells such as keratinocytes, which triggers the downstream activation of IFN stimulate gene factor 3. Upon nuclear translocation of this molecule, there is gene transcription and further activation of immunomodulatory pathways.[39]

There is a role for autostimulatory mechanisms in which type I IFNs released by pDCs can act as agonists for the releasing cell and additional pDCs, ultimately propagating inflammation.[41] Positive improvements in DM symptoms by targeting these upstream signaling molecules and inflammatory cells offer support for the use of JAK inhibitors.

Various cases in which the use of JAK inhibitors such as tofacitinib and ruxolitinib resulted in positive outcomes for DM patients have been reported (Table). Based on significant reduction in Cutaneous Dermatomyositis Disease Area and Severity Index score among patients, the use of these medications was reported as being clinically effective. As described in the Table, patients had improvements in both skin and muscle manifestations of the disease such as reduced pruritus and increased strength.

Scleroderma

Scleroderma is a complex autoimmune disease with various subtypes. This connective tissue disease is broadly categorized as being either systemic or localized. Patients with the systemic variant classically present with calcinosis cutis, Raynaud phenomenon, esophageal dysphagia, sclerodactaly, and telangiectasia's.[1] Cutaneous cases of scleroderma such as localized morphea are more common and present with atrophic violaceous erythema followed by smooth, hard, and depressed yellowish-white or ivory lesions. The pathogenesis is complex, involving damage to vascular endothelium followed by an overactive autoimmune response involving various proteins, cytokines, and immune cells.[2] It is thought that early stages of the disease are predominately Th1- and Th17-mediated, whereas later stages involve Th2 cells predominantly. Effective treatments are available for systemic complications due to scleroderma but less so for cutaneous manifestations of the disease. Currently, it is recommended that patients undergo physical therapy with constant range of motion of all joints, limit exposure to the cold, and refrain from smoking.[2] Systemic corticosteroids have been used, but beneficial outcomes are limited by the risks associated with renal crisis. Newer and evolving therapies include B-cell-depleting therapy (ie, rituximab), transforming growth factor-β1 inhibitors, tyrosine kinase inhibitors (eg, imatinib), and histone deacetylase inhibitors.[2] Of interest as well is the potential for improvements in skin condition with the use of JAK inhibitor medication. One case report has been published in the literature, which presented positive outcomes in a 27-year-old African American male with systemic sclerosis when treated with tofacitinib (Table). The patient originally presented with a history of salt-and-pepper depigmentation with tightening of skin over his fingers and dorsal hands. Raynaud phenomenon, digital ulceration, and various systemic symptoms such as acral paresthesia, unexplained weight loss, constipation, and intractable heartburn were present in this patient. As outlined in the report and highlighted in the Table, the patient promptly noticed improvements in both his skin and joints. It was concluded that JAK inhibitors seem promising as a treatment for fibrosing disorders such as morphea and scleroderma.[42]

Limitations

JAK inhibitors could be an alternative option in various dermatologic conditions such as psoriasis, AA, AD, vitiligo, and connective tissue diseases. Because JAK inhibitors are broader, they may be particularly useful when biologic treatments fail. There are still limited data, and randomized controlled comparator trials are needed to truly assess efficacy of this modality.

Potential side effects

Side effects of JAK inhibitors most commonly include infections, headache, and diarrhea. Serious infections, increased cancer risk, anemia, thrombocytopenia, hypercholesterolemia, and hypertension have also been reported.[43,44] Additionally, tofacitinib has been associated with increased risk for herpes zoster when used in patients with psoriasis.[45]

Conclusion

This review article presents the current understanding of the pathophysiology of psoriasis, AD, AA, vitiligo, DM, DLE, and scleroderma. Clinical data support our proposal for the use and continued exploration of JAK inhibitors in these patients.

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