Janus kinase inhibitors in dermatology: Part I. A comprehensive review

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Janus kinase inhibitors in dermatology: Part I. A comprehensive review

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Detroit, Michigan

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) intracellular signaling pathway is utilized by many proinflammatory molecules to mediate downstream effects and activate gene transcription. Activation of the JAK-STAT pathway contributes to a number of inflammatory dermatoses. Clinical trials and smaller studies have demonstrated the efficacy of JAK inhibitors in the treatment of a variety of dermatologic conditions. Here, we review the use of JAK inhibitors for the treatment of a wide range of dermatologic diseases in a two-part review series. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2021.07.002.)

Key words: dermatology; immunodermatology; immunology; JAK inhibitor; JAK-STAT pathway; Janus kinase inhibitor; Janus kinase-signal transducer and activator of transcription pathway; review.

INTRODUCTION

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway is essential for intracellular cytokine signaling mediated by type I and type II cytokine receptors. There are 7 STAT proteins (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6) and 4 JAK kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2 [Tyk2]) that bind directly to the intracellular domain of type I and type II cytokine receptors.1

Upon ligand binding, JAKs are phosphorylated and activated. Activated JAKs then phosphorylate STAT proteins, which subsequently dimerize and translocate to the nucleus where they directly bind to DNA and regulate gene transcription (Fig 1).2 Examples of cytokines that rely on JAK-STAT signaling to mediate downstream effects include interleukin (IL) 2, IL-4, IL-5, IL-6, IL-12, IL-13, IL-23, and interferon alpha/beta, among others (Table I).3

The significance of the JAK-STAT signaling pathway in the regulation of both hematologic and immune function is highlighted by the fact that the gain-of-function mutations in JAK2 contribute to the pathogenesis of polycythemia vera, essential thrombocythosis, and myelofibrosis.7 Loss of function mutations in STAT3 causes autosomal dominant hyperimmunoglobulin E syndrome, formerly called Job syndrome.7

Understanding the role of these signaling pathways in disease pathogenesis paved the way for the development of JAK inhibitors as a new class of therapeutic small-molecule inhibitors (Table II). Although JAK inhibitors have not been approved by the United States Food and Drug Administration for the treatment of any dermatologic diseases, they show immense promise in the field of dermatology.

Part 1 of this comprehensive review series discusses JAK inhibitor therapy currently under investigation for the treatment of atopic dermatitis (AD) and psoriasis. Part 1 also reviews a number of smaller studies supporting the use of JAK inhibitors in a wide range of dermatologic diseases, including lichen planus (LP), lichen planopilaris, hidradenitis suppurativa (HS), graft-versus-host disease (GVHD), and more. Part 2 of this review series focuses on JAK inhibitors for the treatment of alopecia areata, vitiligo, granulomatous disorders, and systemic lupus erythematosus, with an emphasis on safety and special considerations during the novel coronavirus 2019 (COVID-19) pandemic.

AD

The etiology of AD is complex and involves immune dysregulation, barrier defects, genetic...
factors, and environmental triggers. In the acute phase, the JAK-STAT pathway mediates signaling of several important cytokines in AD pathogenesis, including IL-4, IL-5, IL-13, and IL-31. In the chronic phase, T helper (Th)1, Th17, and Th22 cytokine profiles predominate.

A number of clinical trials support the use of JAK inhibitors in AD (Table III).6–10 Both topical (ruxolitinib 1.5% cream twice daily) and oral (baricitinib, abrocitinib, and upadacitinib) JAK inhibitors were found to be effective at reducing pruritus in patients with AD.6,8,9 In clinical trials, a greater proportion of patients taking oral baricitinib, abrocitinib, or upadacitinib achieved a Validated Investigator’s Global Assessment of AD score of clear or almost clear when compared to placebo: (baricitinib 4 mg once daily 16.8% [P < .001]; baricitinib 2 mg once daily 11.4% [P < .05]; placebo 4.8%); (abrocitinib 200 mg once daily 38.1%; abrocitinib 100 mg once daily 28.4%; placebo 9.1%; P < .001); and (upadacitinib 30 mg once daily plus topical corticosteroids 59%, upadacitinib 15 mg once daily plus topical corticosteroids 40%, placebo plus topical corticosteroids 11%; P < .0001).9

The Eczema Area and Severity Index scores were also higher among patients taking oral baricitinib, abrocitinib, and upadacitinib as compared to placebo in the trials, with greater efficacy noted at higher doses.6,9–10 There are exciting developments on the horizon as Pfizer recently completed the JADE COMPARE trial, a phase 3 trial of abrocitinib for moderate-to-severe AD in which there was an active control arm with dupilumab.

**CAPSULE SUMMARY**

- The scope of use for Janus kinase inhibitors in dermatology is constantly evolving and expanding.
- Janus kinase inhibitors show promise in treating a number of dermatologic diseases reviewed in part 1 of this 2-part review series including psoriasis, atopic dermatitis, lichen planus, graft-versus-host disease, dermatomyositis, and more.

JAK-activated cytokine that is produced by Th22 cells and stimulates keratinocyte proliferation. IL-12 and IL-15 signaling through JAK1 and JAK3 also contribute to disease pathogenesis.11

Although tofacitinib, a JAK1/3 inhibitor was approved by the Food and Drug Administration to treat psoriatic arthritis, it was never approved for the treatment of chronic plaque psoriasis due to an underwhelming performance overall in clinical trials.12 A post hoc analysis of the Oral treatment Psoriasis Trial Pivotal 1 and Oral treatment Psoriasis Trial Pivotal 2 demonstrated tofacitinib may be efficacious for nail psoriasis, however. The proportion of patients achieving a ≥50% reduction in the Nail Psoriasis Severity Index score at week 16 was 32.8% (tofacitinib 5 mg twice daily) and 44.2% (tofacitinib 10 mg twice daily), as compared to 12% taking the placebo.13

Newer selective JAK inhibitors may hold greater promise for the treatment of chronic plaque psoriasis. Recently, dual Tyk2/JAK1 inhibitors and selective Tyk2 inhibitors demonstrated promising results for the treatment of psoriasis. It is thought that Tyk2 inhibition may be particularly efficacious by directly suppressing IL12/23 signaling (Table IV).11,14

**JAK INHIBITORS IN SMALLER STUDIES**

In recent years, a number of small published studies have investigated the use of JAK inhibitors for the treatment of a range of dermatologic diseases. The rationale for JAK inhibitor therapy, efficacy, and safety reported in these studies is presented below.

**LP**

Upregulation of activated STAT1 in keratinocytes and elevated levels of IFN-gamma production by lymphocytes were shown in samples of LP as compared to healthy controls.15 Three patients with biopsy-proven, recalcitrant, erosive LP were treated with tofacitinib 5 mg twice daily. Two patients achieved complete or near-complete remission of disease on tofacitinib. The third patient had significant improvement on concomitant therapy with tofacitinib, prednisone, and methotrexate.15 No adverse events were reported.
Lichen planopilaris

In the pathogenesis of lichen planopilaris, there may be a role for increased levels of cytotoxic CD8+ T cells in the infundibulum and bulge, IFN-gamma-driven collapse of immune privilege, increased levels of IL-4, TGF-beta, and peroxisome proliferator-activated receptor gamma, all of which may be potential targets of JAK inhibitor therapy.16-18 In a case series of 10 patients treated with tofacitinib 5 mg twice daily or 3 times daily (as monotherapy or in combination with adjunctive treatments), there was a statistically significant improvement in the Lichen Planopilaris Activity Index score after treatment.16 One patient stopped treatment due to concerns for developing bladder cancer. No other adverse events were reported.

Chronic actinic dermatitis (CAD)

The pathogenesis of CAD is largely unknown, but is postulated to involve the activation of photoallergens that stimulate an aberrant immune response.19 The specific immunologic role of JAK inhibitors in the treatment of CAD has not been fully elucidated. There was a case report of a 60-year-old man with erythrodermic CAD who had near-complete remission of disease at 2 months on tofacitinib 5 mg twice daily or 3 times daily (as monotherapy or in combination with adjunctive treatments), there was a statistically significant improvement in the Lichen Planopilaris Activity Index score after treatment.20 One patient required concomitant prednisone 5 mg daily.27 Adverse events reported included upper respiratory tract infection in 1 patient, urinary tract infection in 1 patient, and reactivation of herpes virus infection in 1 patient.

Drug reaction with eosinophilia and systemic symptoms

The pathogenesis of drug reaction with eosinophilia and systemic symptoms is not fully elucidated but is thought to involve immune mechanisms, including human leukocyte antigen susceptibility to IL-5–driven drug-specific T cells, contributing to the hypereosinophilia noted in this condition.21,22 Other JAK-STAT–dependent cytokines may also play a role, including IL-4 and IL-13.23 In a report of 2 patients with drug reaction with eosinophilia and systemic symptoms who were poorly controlled on prednisone and methotrexate, symptoms resolved on tofacitinib 5 mg twice daily.24 No adverse events were reported.

Hypereosinophilic syndrome

In the lymphocytic subtype, clonal T cells produce Th2 cytokines, including IL-4, IL-5, and IL-13. IL-5 activates eosinophils to release toxic granule contents. IL-4 and IL-13 are thought to contribute to high levels of IgE.25 Recent work demonstrated STAT3 gain-of-function mutations as well as upregulation of STAT3 gene targets promoted Th2 cell differentiation and the production of eosinophil-promoting Th2 cytokines in patients with the lymphocytic subtype of hypereosinophilic syndrome.26 Remission or near-complete remission of disease was achieved for all patients in a case report of 5 patients treated with either tofacitinib 5 mg twice daily (4 patients) or ruxolitinib 25 mg in the morning and 10 mg at night (1 patient). One patient required concomitant prednisone 5 mg daily.27 Adverse events reported included upper respiratory tract infection in 1 patient, urinary tract infection in 1 patient, and reactivation of herpes virus infection in 1 patient.

Acute and chronic GVHD

Important inflammatory cytokines implicated in the pathogenesis of GVHD include IL-1, IL-6, IFN-gamma, and tumor necrosis factor-alpha.28 Autocrine IL-2 production stimulates T-cell activation and proliferation, perpetuating the inflammatory cycle in GVHD.29 JAK inhibitors may dampen this inflammatory immune response.

In a multicenter, phase 2 trial of 71 patients with steroid refractory acute GVHD treated with oral ruxolitinib starting at 5 mg daily plus corticosteroids (REACH1), 39 patients (54.9%; 95% confidence interval, 42.7%-66.8%) achieved an overall response at day 28. Complete response was observed in 19 patients (26.8%) and 61.1% achieved a skin-specific response. The most common hematologic adverse events were anemia (64.8%), thrombocytopenia (62%), and neutropenia (47.9%). The most common infectious adverse event was cytomegalovirus infection (19.7%).30 In a multicenter, randomized, phase 3 trial comparing the efficacy and safety of ruxolitinib 10 mg twice daily for steroid refractory acute GVHD (REACH2), the overall response at day 28 was higher for the ruxolitinib group as compared to

Abbreviations used:

AD: atopic dermatitis
CAD: chronic actinic dermatitis
GVHD: graft-versus-host disease
HS: hidradenitis suppurativa
IFN: Interferon
IL: Interleukin
JAK-STAT: Janus kinase–signal transducer and activator of transcription
LP: lichen planus
Tyk2: tyrosine kinase 2
Th: T helper
placebo [96/154 (62%), ruxolitinib 10 mg twice daily] versus [61/155 (39%), placebo], odds ratio 2.64; 95% confidence interval, 1.65-4.22; *P* < .001. The skin staging also improved from baseline to day 28. The most common adverse event was thrombocytopenia in 50 of 152 (33%) of the ruxolitinib group as compared to 27 of 150 (18%) of the control group, followed by anemia in 46 of 152 (30%) of the ruxolitinib group as compared to 42 of 50 (28%) of the control group.31

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**Fig 1.** Janus kinase (JAK)-signal transducer and activator of transcription (JAK-STAT) pathway. *P*, Phosphorylation.

**Table I.** JAK proteins and associated cytokines that signal through each protein

<table>
<thead>
<tr>
<th>JAK protein</th>
<th>Cytokines</th>
</tr>
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<tbody>
<tr>
<td>JAK1</td>
<td>IFN-alpha, IFN-beta, IFN-gamma, IL-2, IL-4, IL-6, IL-7, IL-9, IL-10, IL-11, IL-13, IL-15, IL-19, IL-21, IL-22, IL-27, IL-28, IL-29, and IL-35</td>
</tr>
<tr>
<td>JAK2</td>
<td>IL-3, IL-5, IL-6, IL-10, IL-11, IL-13, IL-12, IL-19, IL-22, IL-23, IL-27, IL-35, IFN-gamma, GM-CSF, G-CSF, EPO, GH, TPO, and leptin</td>
</tr>
<tr>
<td>JAK3</td>
<td>IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, and IL-21</td>
</tr>
<tr>
<td>Tyk2</td>
<td>IFN-alpha, IFN-beta, IL-6, IL-10, IL-11, IL-12, IL-19, IL-22, IL-23, IL-27, IL-28, and IL-29</td>
</tr>
</tbody>
</table>

*EPO*, Erythropoietin; *G-CSF*, granulocyte colony-stimulating factor; *GH*, growth hormone; *GM-CSF*, granulocyte-macrophage colony-stimulating factor; *IFN*, interferon; *IL*, interleukin; *JAK*, Janus kinase; *TPO*, thrombopoietin; *Tyk2*, tyrosine kinase 2.
Table II. Indication and mechanism of action of oral JAK inhibitors that are approved by the United States Food and Drug Administration for use in humans

<table>
<thead>
<tr>
<th>JAK Inhibitor</th>
<th>Mechanism of action</th>
<th>Indications</th>
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</thead>
<tbody>
<tr>
<td>Ruxolitinib</td>
<td>JAK 1/2</td>
<td>Myelofibrosis, Polycythemia vera, Acute graft-versus-host disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psoriatic arthritis, Rheumatoid arthritis, Ulcerative colitis*</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>JAK 1/3</td>
<td>Psoriatic arthritis, Rheumatoid arthritis, Ulcerative colitis*</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>JAK 1/2</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Upadacitinib</td>
<td>JAK 1</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Fedratinib</td>
<td>JAK 2</td>
<td>Myelofibrosis</td>
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</tbody>
</table>

*JAK, Janus kinase.

*In 2019 the Food and Drug Administration placed a black box warning for the drug’s 10 mg twice daily dose for ulcerative colitis.

Table III. JAK inhibitors investigated for the treatment of atopic dermatitis

<table>
<thead>
<tr>
<th>JAK inhibitor under investigation</th>
<th>Study design</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib 1.5% cream</td>
<td>Phase 2 clinical trial*</td>
<td>Patients using ruxolitinib 1.5% cream twice daily had a significantly reduced itch numerical rating score as compared to vehicle control (-1.8 vs -0.2, P &lt; .001)</td>
<td>The most common adverse events were application site burning (2/126 [1.6%], vehicle) vs (2/253 [0.8%], ruxolitinib 1.5% cream) and application site pruritus, (2/126 [1.6%], vehicle) vs (0/253 [0%], ruxolitinib 1.5% cream)</td>
</tr>
<tr>
<td>Oral baricitinib 1 mg, 2 mg, or 4 mg once daily</td>
<td>Two independent, multicenter, double-blind, phase 3 trials; BREEZE-AD 1 and BREEZE-AD 2*</td>
<td>The proportion of patients achieving a 75% improvement in EASI score was significantly higher among patients taking baricitinib 4 mg daily (24.8 in BREEZE-AD1, P &lt; .001; 21.1 in BREEZE-AD2, P &lt; .001) as compared to placebo (8.8 in BREEZE-AD 1; 6.1 in BREEZE-AD 2)</td>
<td>Nasopharyngitis was the most common adverse event in both trials with the results from BREEZE-AD 1 reported here: (22/127 [17.3%], baricitinib 1 mg once daily) vs (12/123 [9.8%], baricitinib 2 mg once daily), (12/125 [9.6%], baricitinib 4 mg once daily), (26/249 [10.4%], placebo)</td>
</tr>
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<td></td>
<td></td>
<td>Other common adverse events reported in both trials with comparable results were oral herpes simplex viral infection, headache, and diarrhea</td>
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<td>One patient with a history of tobacco use on baricitinib 4 mg daily concurrently with oral contraceptives developed a pulmonary embolism with subsequent recovery after discontinuation of therapy.</td>
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<td></td>
<td></td>
<td>No malignancies, deaths, or severe cardiovascular events were reported</td>
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</table>

*Continued*
JAK inhibitors also proved to be efficacious in the treatment of chronic GVHD. In a study of 19 patients with steroid-dependent chronic GVHD, ruxolitinib 5 mg twice daily lead to complete response in 14 of 17 patients with nonsclerodermatous cutaneous GVHD. No infections or cytopenias were noted in the study.32

Morphea and eosinophilic fasciitis
JAK inhibition of IL-4 and TGF-beta signaling may inhibit collagen production and fibroblast-derived extracellular matrix proteins.33 There was a report of a patient with diffuse morphea who had significant improvement of cutaneous induration after 1 year of tofacitinib 5 mg twice daily and prednisone 10 mg daily.

A patient with eosinophilic fasciitis had marked improvement of cutaneous induration on tofacitinib 5 mg twice daily and methotrexate 10 mg weekly as well as a 3-month prednisone taper that started at 15 mg daily.33 Adverse events were not reported.

Dermatomyositis
Patients were found to have down regulation of STAT 1 signaling after JAK inhibitor therapy as well as

<table>
<thead>
<tr>
<th>JAK inhibitor under investigation</th>
<th>Study design</th>
<th>Results</th>
<th>Safety</th>
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<tbody>
<tr>
<td><strong>Oral abrocitinib</strong>&lt;br&gt;100 mg or 200 mg once daily</td>
<td>Phase 3 randomized clinical trial9</td>
<td>The EASI score at 12 weeks was (94/154 [61%], abrocitinib 200 mg once daily) vs (69/155 [44.5%], abrocitinib 100 mg once daily) vs (8/77 [10.4%], placebo), P &lt; .001</td>
<td>The most frequently reported adverse events were nausea (22/155 [14.2%], abrocitinib 200 mg once daily), nasopharyngitis (20/158 [12.7%], abrocitinib 100 mg once daily), and atopic dermatitis (12/78 [15.4%], placebo)</td>
</tr>
<tr>
<td><strong>Oral upadacitinib</strong>&lt;br&gt;15 mg or 30 mg once daily plus topical corticosteroids</td>
<td>Phase 3 randomized clinical trial10</td>
<td>The EASI-75 score at 16 weeks was (194/300 [65%], upadacitinib 15 mg once daily plus topical corticosteroids) vs (229/297 [77%], upadacitinib 30 mg once daily plus topical corticosteroids) vs (80/304 [38.1%] placebo plus topical corticosteroids), P &lt; .0001 for both doses of upadacitinib&lt;br&gt;Serious adverse events leading to study discontinuation occurred in (4/300 [1%], upadacitinib 15 mg once daily) vs (4/297 [1%], upadacitinib 30 mg once daily) vs (7/303 [2%], placebo)&lt;br&gt;The most frequently reported adverse events were acne and nasopharyngitis. Rates of acne were as follows: (30/300 [10%], upadacitinib 15 mg once daily plus topical corticosteroids) vs (41/297 [14%], upadacitinib 30 mg once daily plus topical corticosteroids) vs (6/303 [2%], placebo plus topical corticosteroids). Rates of nasopharyngitis were as follows: (37/300 [12%], upadacitinib 15 mg once daily) vs (40/297 [14%], upadacitinib 30 mg once daily) vs (34/303 [11%], placebo)&lt;br&gt;One patient taking upadacitinib 30 mg once daily plus topical corticosteroids developed a keratoacanthoma&lt;br&gt;Elevated creatinine phosphokinase levels, and anemia were infrequent and reported in both the placebo and treatment groups</td>
<td></td>
</tr>
</tbody>
</table>

EASI, Eczema Area and Severity Index; JAK, Janus kinase; BREEZE-AD1 and BREEZE-AD2, A Study of Baricitinib (LY3009104) in Patients With Moderate to Severe Atopic Dermatitis.
down regulation of IFN-gamma related genes and chemokine C-X-C motif ligand (CXCL) 9 and 10.34
In an open-label 12-week pilot study of 10 patients with dermatomyositis taking tofacitinib 11 mg daily extended release, 50% experienced moderate improvement in disease activity and 50% achieved minimal improvement, according to the 2016 American College of Rheumatology/European League Against Rheumatism myositis response criteria.34
No serious adverse events were reported. One patient developed recurrent urinary tract infections. There were no alterations in white blood cell count, hemoglobin level, creatinine kinase, serum creatinine, or platelet count over the course of the study.

Table IV. JAK inhibitors investigated for the treatment of psoriasis

<table>
<thead>
<tr>
<th>JAK inhibitor under investigation</th>
<th>Study design</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF-06700841 (an oral Tyk2/JAK1 inhibitor) 30 mg once daily or 100 mg once daily</td>
<td>Phase 1 randomized clinical trial11</td>
<td>Maximal mean percent change from baseline in the TPSS was significantly better than placebo: -70.8% (30 mg once daily) and -92.5% (100 mg once daily) vs approximately 20% (placebo)</td>
<td>Increased serum creatinine levels (n = 5), neutropenia (n = 1), and decreased neutrophil count (n = 1)</td>
</tr>
<tr>
<td>BMS-986165 (a selective Tyk2 inhibitor) 3 mg every other day, or 3 mg once daily, or 3 mg twice daily, or 6 mg twice daily, or 12 mg once daily</td>
<td>Phase 2 double-blind clinical trial14</td>
<td>≥75% reduction in PASI at week 12 was 7% (placebo), 9% (3 mg every other day, P = .49 vs placebo), 39% (3 mg once daily, P &lt; .001 vs placebo), 69% (3 mg twice daily, P &lt; .001 vs placebo), 67% (6 mg twice daily, P &lt; .001 vs placebo), and 75% (12 mg once daily, P &lt; .001 vs placebo)</td>
<td>Nasopharyngitis, headache, diarrhea, nausea, and URI were the most common adverse events</td>
</tr>
</tbody>
</table>

JAK1, Janus kinase 1; PASI, Psoriasis Area Severity Index; TPSS, target plaque severity score; Tyk2, tyrosine kinase 2; URI, upper respiratory tract infection.

One patient developed uncomplicated herpes zoster reactivation.

Conclusions and future directions
JAK inhibitors exploded onto the scene in dermatology several years ago and are currently under investigation for the treatment of a wide range of dermatologic diseases. The newer, more-selective second-generation JAK inhibitors may be particularly important going forward. The selective JAK 1 inhibitors upadacitinib and abrocitinib are currently being studied in clinical trials for AD and abrocitinib demonstrated efficacy in treating adults with moderate-to-severe AD.16 Similarly, selective oral Tyk2 inhibitors at a dose of 3 mg daily and higher proved efficacious in treating adults with moderate-to-severe psoriasis over a 12-week period.14 These selective JAK inhibitors have the potential to drastically change the therapeutic landscape for inflammatory dermatoses and hold immense promise for patients and dermatologists alike.

Conflicts of interest
None declared.

REFERENCES


