doi:10.36849/JDD.2021.NVRM7032

NEWS, VIEWS, & REVIEWS

Off-Label Uses of JAK Inhibitors in Dermatology

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Introduction

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is a crucial component of immune function, and JAK inhibitors allow dermatologists to regulate this pathway in certain disease states. Once bound to ligands, JAKs phosphorylate cytokine receptors and STAT proteins, which translocate to the nucleus and activate transcription of immunologic proteins.[1] Four JAK isoforms have been identified: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). The different isoforms bind varyingly to cytokines including interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21. While the first-generation JAK inhibitors — tofacitinib, ruxolitinib, and baricitinib — block multiple JAK isoforms, second generation JAK inhibitors, such as decernotinib, abrocitinib, and upadacitinib, target a particular JAK, reducing adverse effects.

The first Food and Drug Administration (FDA)-approved JAK inhibitor, ruxolitinib, was originally for the treatment of myelofibrosis, and now topical ruxolitinib is approved for both atopic dermatitis (AD) and vitiligo. Abrocitinib and upadacitinib are approved for the treatment of AD. Tofacitinib is approved for the treatment of psoriatic arthritis (PsA) and currently studied in psoriasis, alopecia areata (AA), and AD.[2] Baricitnib is the most recent addition to the JAK inhibitors approved for dermatologic use, specifically for AA. The ability of JAK inhibitors to modulate immune function make them ideal therapies for numerous dermatoses, many of which have yet to be FDA approved; therefore, JAK inhibitors are becoming more important than ever for dermatologists to have in their treatment armamentarium. This review examines the off-label uses and possible future indications of JAK inhibitors in dermatology summarized in Table 1.

Alopecia Areata

With baricitinib, JAK inhibitors have introduced the first FDA-approved therapy for AA. Other JAK inhibitors have been investigated and some are aiming to seek approval for AA. Studies indicate tofacitinib 5 mg twice daily and ruxolitinib 15 to 25 mg twice daily induce significant hair regrowth in patients with AA after 3 to 6 months.[3] Other studies with topical tofacitinib 1%-2% and ruxolitinib 0.6%-2% both applied twice daily also indicate success in 3 to 6 months, however to a lesser extent than oral therapies.[4]

Dermatomyositis

The majority of reports of the use of JAK inhibitors in dermatomyositis (DM) involve oral ruxolitinib or tofacitinib and indicate significant improvement.[5] Specifically, tofacitinib 11 mg extended release given daily to patients with DM resulted in

Table 1. Dermatologic uses for JAK inhibitors

Drug	Delivery	5-10 mg twice daily/ 11 mg extended release	Approved Indication	Off-Label Uses
Tofacitinib	Oral	1%-2% twice daily	PsA	AA, DM, GVHD, GA, HS, LP, NL, Psoriasis, PG, Sarcoidosis, SLE/CLE, Morphea/Systemic Sclerosis, Vitiligo
	Topical	10-25 mg twice daily	--	AA,Vitiligo
Ruxolitinib	Oral	0.6%-2% twice daily	--	AA, DM, GVHD, NL, Sarcoidosis, Morphea/Systemic Sclerosis, Vitiligo
	Topical	2-8 mg daily	AD	AA, Psoriasis
Baricitinib	Oral	100-200 mg daily	AA	Psoriasis, PG, SLE, Morphea/Systemic Sclerosis, Vitiligo
Abrocitinib	Oral	15-30 mg daily	AD	-
Upadacitinib	Oral		AD	HS

Abbreviations
AA - Alopecia Areata
AD - Atopic Dermatitis
CDASI - Cutaneous Dermatomyositis Disease Area and Severity Index
CLE - Cutaneous Lupus Erythematosus
DM - Dermatomyositis
ELP - Erosive Lichen Planus
FDA - Food and Drug Administration

significantly reduced Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) scores after 3 months (mean ± SD 28 ± 15.4 at baseline versus 9.5 ± 8.5 at 12 weeks) (P=0.0005).[6] Recalcitrant juvenile and adult DM treated with ruxolitinib 10 to 15 mg twice daily for 6 to 12 months was successful in multiple case reports and series.[7-9]

Graft-Versus-Host Disease

Graft-versus host disease (GVHD) frequently results in cutaneous involvement and in treatment-resistant patients, oral ruxolitinib 10 mg twice daily has been reported to improve symptoms within 1 to 2 weeks.[10] Studies in mouse models of GVHD show that tofacitinib similarly treats GVHD and actually prevents GVHD by modulating the CD8 T-cell response following bone marrow transplants.[11]

Granuloma Annulare

Granuloma annulare (GA) is another cutaneous disease for which little progress has been witnessed in treatment options, though JAK inhibitors may change this soon. Multiple cases and studies with tofacitinib for GA indicate promising results.[12] Tofacitinib 5 mg twice daily led to a significant improvement in GA after 6 months, such that 3 of 5 patients treated experienced complete GA resolution, and the remaining 2 patients experienced 61%-70% reduction in body surface area involvement.[13]

Hidradenitis Suppurativa

In a case series of 2 patients with treatment-resistant hidradenitis suppurativa (HS), tofacitinib 5 mg twice daily reduced ulceration, drainage, and pain after 3 to 4 months and allowed other therapies, like cyclosporine, to be discontinued.[14] One study found significant benefit in patients with HS who were treated with upadacitinib 15 mg daily after several months, and therefore upadacitinib is currently in phase II trials for HS.[15,16]

Lichen Planus

JAK inhibitors also show promise in treating lichen planus (LP), particularly erosive lichen planus (ELP) and lichen planopilaris (LPP). One case series of 3 patients with LP and ELP treated with tofacitinib 5 mg twice daily noted significant improvement of symptoms within 1 to 3 months.[17] Similarly, another case series of LPP patients treated with tofacitinib 5 mg twice to three times daily showed success in 80% of patients after 6 to 12 months, and noted that some patients who did not respond to 5 mg twice daily did respond to 5 mg 3 times daily.[18]

Necrobiosis Lipoidica

Success in treating necrobiosis lipoidica (NL) with JAK inhibitors has been reported in a few cases. One patient with polycythemia vera (PV) and NL treated with ruxolitinib 10 mg twice daily experienced almost complete resolution of active NL after 3 months.[19] Additionally, another patient treated with tofacitinib 5 mg twice daily and intralesional corticosteroids had complete re-epitheliazation of prior ulcerations after 6 weeks.[20]

Psoriasis

Tofacitinib is approved for PsA and reports indicate that successful treatment of PsA also improves comorbid plaque psoriasis.[21] After 16 weeks, 40% of patients taking tofacitinib 5 mg twice daily achieved a psoriasis area and severity index (PASI) score of 75, and 59% of those at the 10-mg twice daily dosing achieved a PASI75.[22] A meta-analysis of 3743 psoriasis patients treated with tofacitinib 5 to 10 mg twice daily concluded that tofacitinib was safe and effective at treating plaque psoriasis.[23] Comparably, after 12 weeks, 43% of patients treated with baricitinib 8 mg daily achieved a PASI75, as did 54% of the patients in the 10 mg daily group. Topical ruxolitinib 0.5%-1.5% has also been studied in psoriasis, and while efficacy of the lower dose was similar to vehicle, the 1.0% and 1.5% dosages resulted in 53% and 54% reduced lesion scores compared to 32% for the vehicle.[24]

Pyoderma Gangrenosum

In a case series of 2 patients with treatment resistant pyoderma gangrenosum (PG), baricitinib 4 mg lead to resolution and re-epithelization of a scalp PG in 5 weeks and lower leg PG in 3 months.[25] Similarly, 3 patients with Crohn's disease and treatment-resistant PGs were started on tofacitinib 5 mg twice daily and all 3 patients experienced resolution within 1 to 3 months on therapy.[26]

Sarcoidosis

Sarcoidosis is another T-cell mediated dermatosis that is responsive to inhibition of the JAK pathway. Specifically tofacitinib 5 mg twice daily for 3 months lead to resolution of cutaneous lesions in 3 to 10 months.[12,27,28] In another case report, ruxolitinib 10 mg twice daily for PV resulted in resolution of the patients cutaneous sarcoidosis after 5 months.[29]

Systemic and Cutaneous Lupus

An altered JAK/STAT pathway has been implicated in the pathophysiology of systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE).[30] One clinical trial with baricitnib found that a 2-mg daily dose did not improve symptoms of SLE, whereas a 4-mg daily dose resolved symptoms of arthritis and skin rashes.[31] In a case series of 3 patients with CLE, tofacitinib 5 mg twice daily resulted in resolution of skin lesions within 4 to 7 months.[32]

Morphea/Systemic Sclerosis

Morphea and systemic sclerosis was found to respond well to JAK inhibition; specifically tofacitinib 5 to 10 mg twice daily, baricitnib 2 to 4 mg daily, and ruxolitinib 10 mg twice daily have been reported as successful therapies for morphea and

systemic sclerosis leading to decreased skin tightness and improvement in mobility within several weeks depending on severity and the affected areas.[33]

Vitiligo

Oral and topical tofacitinib as well as oral ruxolitinib and baricitinib were found to be safe and effective for the treatment of vitiligo. Dosages included tofacitinib 5 to 10 mg twice daily, tofacitinib 2%, baricitinib 4 mg daily, and ruxolitinib 20 mg twice daily. Repigmentation occurred within 4 to 10 months depending on severity and location.[34]

Safety Concerns

The most common adverse events reported with JAK inhibitor use are anemia, thrombocytopenia, urinary tract infections, dizziness, and headaches. More serious adverse effects include reactivation of hepatitis B virus or herpes simplex virus, disseminated tuberculosis, and increase in risk of skin cancers, likely secondary to the immunosuppressive effects. The FDA approved a Boxed Warning for tofacitinib in 2019 after a postmarketing safety clinical trial showed an increased risk of cardiac adverse events, blood clots, cancer, and death, particularly at doses of tofacitinib 10 mg twice daily compared to patients taking a tumor necrosis factor inhibitor.[35] Further research is needed to determine the efficacy, route of delivery, and optimal dosage for treating dermatologic conditions with JAK inhibitors.

Conclusion

Separate from the dermatologic indications for which JAK inhibitors are currently approved, much of the evidence for use in off-label dermatoses is summarized in this review. In addition, singular case reports exist utilizing JAK inhibitors for chronic urticaria, Sjögren's syndrome, hypereosinophilic syndrome, chronic mucocutaneous candidiasis, pembrolizumab-induced cutaneous lesions, Behcet's syndrome, and synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome.[36-42] While JAK inhibitors can successfully treat numerous dermatologic conditions, potential adverse events associated with these medications must be weighed against possible benefits, and, most importantly, an informed discussion should take place with patients regarding potential adverse events. For many difficult-to-treat conditions, JAK inhibitors may transform treatment paradigms; however, further research and studies should be undertaken to elucidate the real-world efficacy and safety profiles of these new therapies.

Disclosure

The authors declare no conflicts of interest.

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