

JAK INHIBITORS AND TYK-2 INHIBITORS IN DERMATOLOGY (LITERATURE REVIEW)

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Annotation

Monitoring and safety recommendations for primary care clinicians regarding Janus kinase (JAK) and tyrosine kinase 2 (TYK2) inhibitors in inflammatory skin disorders remain insufficiently defined [1, 2]. This review summarizes clinically relevant and updated guidance on the monitoring, efficacy, and safety profiles of these agents. A systematic review of PubMed and U.S. Food and Drug Administration (FDA)–approved drug labeling was conducted to integrate current evidence [1, 3]. JAK and TYK2 inhibitors have recently received FDA approval for several immune-mediated dermatologic diseases, including atopic dermatitis, plaque psoriasis, alopecia areata, and vitiligo [3–5]. Owing to their mechanism of blocking intracellular cytokine signaling, these drugs provide potent anti-inflammatory effects but carry boxed warnings concerning major adverse cardiovascular events (MACE), venous thromboembolism (VTE), serious infections, and malignancy [4, 6]. Therefore, regular clinical and laboratory monitoring—complete blood count, liver enzymes, lipid levels, and infection risk assessment—is strongly advised [6, 7].

Although these therapies are usually initiated by dermatologists, increasing clinical use necessitates that primary care clinicians remain familiar with safety monitoring and adverse-event recognition [1, 6]. Next-generation selective TYK2 inhibitors, such as deucravacitinib, exhibit comparable efficacy with a more favorable safety profile than first-generation JAK inhibitors [7, 8]. As use expands, collaboration between specialists and primary physicians will be essential to optimize patient outcomes and ensure ongoing pharmacovigilance [1, 2, 6].

Keywords: Vitiligo, alopecia areata, psoriasis vulgaris, Janus Kinase inhibitors, psoriasis, tyrosine-protein kinase inhibitors,

Introduction

Janus kinase (JAK) inhibitors and tyrosine Kinase 2 (TYK2) inhibitors are classes of small molecule inhibitors that have displayed promising data when it comes to the treatment of inflammatory skin diseases including atopic dermatitis (AD), plaque psoriasis, alopecia areata (AA), and vitiligo.[10] Medications within the JAK inhibitor and TYK2 inhibitor classes have gained approval from the U.S. Food and Drug Administration (FDA) for the management of select inflammatory skin conditions and further approvals are underway.[10]

JAK inhibitors have become more common in the dermatologic therapeutic landscape, which makes understanding this class of medication important for family medicine physicians. Although there are recommended monitoring and safety guidelines produced by the manufacturer of each drug, long-term safety monitoring and laboratory screenings are largely provider-dependent as well as initiation and discontinuation of the drug per those laboratory findings and patient disease course. The reason for such emphasis on monitoring and safety guidelines is in part due to the box warning associated with the JAK inhibitors, which also warrants further discussion regarding the original studies completed and implications for specific patient populations.[11] Although there exists warranted concern and a need for continued understanding regarding long-term effects and best practices surrounding these medications, the efficacy and overall safety profile justify conversation and education outside of the dermatologic field due to the life-changing results these medications offer patients living with inflammatory skin conditions. In this article, we provide a brief review to help familiarize the primary care physician with the dermatologic applications and safety of JAK and TYK2 inhibitors. We aim to emphasize the important need for continued research as well as education regarding indications, comparative analysis of other current treatment modalities, and monitoring of these medications.

The Janus kinase signaling pathway

The JAK family consists of four non-receptor tyrosine kinases—JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2)—each encoded by distinct genes and characterized by seven conserved JAK homology (JH) domains [13]. The JH1 domain confers catalytic kinase activity, while the adjacent pseudokinase (JH2) domain modulates kinase function via autoinhibition and allosteric regulation [14].

JAKs are constitutively associated with the intracellular domains of type I and type II cytokine receptors, which lack intrinsic kinase activity [15]. These receptors include those for interleukins (IL-2, IL-4, IL-6, IL-12, IL-23), interferons (IFN- α , IFN- β , IFN- γ), growth hormones, and erythropoietin.

The downstream transcription factors, STAT1–STAT6, are latent cytoplasmic proteins that possess an SH2 domain (for receptor docking), a DNA-binding domain, and a C-terminal tyrosine residue that becomes phosphorylated upon activation [16]. Upon cytokine binding to its cognate receptor, ligand-induced receptor dimerization or oligomerization brings two receptor-associated JAK molecules into proximity, enabling auto- and trans-phosphorylation on activation loop tyrosines (e.g., Tyr1007/Tyr1008 in JAK2) [17].

Activated JAKs then phosphorylate specific tyrosine residues on the receptor's cytoplasmic tails, creating high-affinity docking sites for STAT proteins via their SH2 domains [18].

Once recruited, STATs themselves are phosphorylated by JAKs at conserved tyrosine residues (e.g., Tyr701 in STAT1, Tyr705 in STAT3), allowing them to dissociate from the receptor complex, dimerize via reciprocal SH2–pTyr interactions, and translocate into the nucleus [19].

Inside the nucleus, STAT dimers bind to gamma-activated sequence (GAS) or interferon-stimulated response elements (ISRE) in the promoter regions of target genes, initiating transcriptional programs that regulate cell proliferation, differentiation, apoptosis, and cytokine production [12, 20].

Janus kinase inhibitors and tyrosine kinase 2 inhibitors

Janus kinase inhibitors work by inhibiting one or more JAK proteins in the JAK/STAT cascade, giving them various impacts such as immunomodulatory and anti-inflammatory effects. Specifically, this mechanism allows the hindrance of proinflammatory cytokines and T-cell activity, which has been found to have significant benefits in treating certain inflammatory skin conditions.[22] Additionally, TYK2 inhibitors are orthosteric inhibitors that impede adenosine triphosphate (ATP) binding to the JH1 catalytic domain and are not entirely selective.[23]

Deucravacitinib, the only TYK2 FDA-approved for the treatment of moderate to severe plaque psoriasis, is an allosteric inhibitor that binds to the pseudokinase JH2 domain of TYK2. This allows for greater selectivity and reduces the risk of adverse events.[23] Ritlecitinib is a JAK inhibitor, approved for alopecia, that targets JAK3 as well as TEC kinase. TEC kinase is a subgroup of non-receptor protein tyrosine kinases. It is associated with intracellular signaling for many pathways including inflammatory responses.[24] An overview of the JAK and TYK2 inhibitors approved by the FDA for the inflammatory conditions focused on in this review, as well as associated cytokines and systems affected, are provided in Table 1 and 2 below[1].

Table 1: Janus kinase inhibitors and tyrosine kinase 2 inhibitors FDA approved in US for inflammatory skin conditions

Compound with brand name	Target	Formulation	FDA-approved indications
Topical Ruxolitinib (Opzelura™)	JAK1, 2	Cream	Atopic dermatitis and Non-segmental vitiligo in adults and adolescents 12 years of age and older[7]

Oral

Abrocitinib (Cibinqo™)	JAK1	Tablet	Atopic dermatitis in adults and adolescents 12 years of age and older[8]
Baracitinib (Olmiant®)	JAK1, 2	Tablet	Alopecia areata in adults 18 years of age and older[9]
Deucravacitinib (Sotyktu™)	TYK2	Tablet	Plaque psoriasis in adults 18 years of age and older[10]
Ritlecitinib (Litfulo™)	JAK3, TEC-kinase	Capsule Extended-r	Severe alopecia areata in adults and adolescents 12 years of age and older[11]
Tofacitinib (Xeljanz®)	JAK1, 2 JAK 1	release tablet	Psoriatic arthritis in adults and children 2 years of age and older[12]
Upadacitinib (Rinvoq®)		Tablet	Atopic dermatitis in adults and adolescents 12 years of age and older[13]

Table 2: JAK and TYK2 inhibitors with associated cytokine activity and systems impacted based on target protein

Medication with brand name	Target protein with associated cytokine activity and systems impacted[14]
Topical	
Ruxolitinib (Opzelura™)	JAK 1: Type I IFN, IFN-γ, IL-6, IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 JAK 2: IL-23, IL-12, IFN-γ, IL-6, EPO, GH, GM-CSF, TPO, leptin, prolactin. IL-3, IL-5 Immune system, blood cell development, metabolic activity, lipid metabolism
Systemic	
Abrocitinib (Cibinqo™)	JAK 1: Type I IFN, IFN-γ, IL-6, IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 Immune system, metabolic activity, lipid metabolism
Baracitinib (Olmiant®)	JAK 1: Type I IFN, IFN-γ, IL-6, IL-2, IL-4, IL-7, IL-9, IL-15, IL-21

Deucravacitinib (Sotyktu™)

Ritlecitinib (Litfulo®)

Tofacitinib (Xeljanz®)

Upadacitinib (Rinvoq®)

JAK 2: IL-23, IL-12, IFN- γ , IL-6, EPO,
GH, GM-CSF, TPO, leptin, prolactin,
IL-3, IL-5

Immune system, blood cell development,
metabolic activity, lipid metabolism

TYK2: IL-23, IL-12, Type I IFN

Immune system

JAK3: IL-2, IL-4, IL-7, IL-9, IL-15, IL-21

Immune system, metabolic activity

JAK 1: Type I IFN, IFN- γ , IL-6, IL-2,
IL-4, IL-7, IL-9, IL-15, IL-21

JAK 2: IL-23, IL-12, IFN- γ , IL-6, EPO,
GH, GM-CSF, TPO, leptin, prolactin,
IL-3, IL-5

Immune system, blood cell development,
metabolic activity, lipid metabolism

JAK 1: Type I IFN, IFN- γ , IL-6, IL-2,
IL-4, IL-7, IL-9, IL-15, IL-21

Immune system, metabolic activity, lipid
metabolism

Vitiligo

Vitiligo is an autoimmune skin disorder characterized by selective destruction of melanocytes, leading to depigmented patches. Immune dysregulation, particularly involving CD8⁺ T cells, IFN- γ , and IL-15 signaling, drives melanocyte apoptosis. Recent research indicates that the **JAK–STAT pathway** plays a central role in this process: IFN- γ activates JAK1/2 in T cells, which phosphorylates STAT1, promoting transcription of chemokines (e.g., CXCL10) that recruit cytotoxic T cells to melanocytes. This immunological cascade results in localized depigmentation [25,26]. JAK inhibitors block phosphorylation events at the receptor level, preventing STAT activation and subsequent transcription of pro-inflammatory genes. By inhibiting JAK1/2 (or selectively TYK2), these agents interrupt the IFN- γ /IL-15-driven recruitment of cytotoxic T cells, effectively reducing melanocyte destruction. Topical formulations deliver local inhibition, while systemic administration can target widespread disease [27,28]. **Topical therapy:** Ruxolitinib cream (JAK1/2 inhibitor) has demonstrated significant facial and body repigmentation in multiple phase II and III trials. Mean VASI (Vitiligo Area Scoring Index) improvements ranged from 30–45%

after 24 weeks. **Systemic therapy:** Oral JAK inhibitors combined with narrow-band UVB phototherapy show synergistic effects, enhancing repigmentation in extensive vitiligo. **Safety profile:** Topical JAK inhibitors generally cause mild, localized reactions (e.g., erythema, pruritus). Systemic therapy carries risks such as immunosuppression, infection, thrombosis, and elevated cardiovascular risk. Long-term safety data remain limited [29]. JAK–STAT inhibitors represent a significant advancement in vitiligo therapy. Topical formulations, especially ruxolitinib, offer clinically meaningful repigmentation with a favorable safety profile. Systemic inhibitors show promise for extensive disease, but careful monitoring and further long-term studies are necessary to define optimal dosing and safety. Continued research is likely to expand the therapeutic repertoire, including TYK2-selective agents and combination strategies.

Plaque psoriasis

Plaque psoriasis (psoriasis vulgaris) is a chronic autoimmune skin disorder characterized by keratinocyte hyperproliferation, erythematous plaques, and scaling. Dysregulation of T-helper 17 (Th17) and Th1 immune pathways leads to overproduction of cytokines such as IL-23, IL-12, IL-17, TNF- α , and type I/II interferons. The **JAK–STAT pathway** serves as a crucial intracellular signaling mechanism, translating cytokine receptor engagement into transcriptional activation of pro-inflammatory and proliferative genes. Recent studies indicate that the IL-23/Th17 axis signals via TYK2-mediated JAK–STAT activation, promoting keratinocyte proliferation and immune cell infiltration in psoriatic plaques. Targeting TYK2 can therefore selectively suppress these pathways while sparing other JAK-dependent immune functions [30,31]. JAK inhibitors block the phosphorylation of JAK kinases at cytokine receptor complexes, preventing downstream STAT activation and transcription of inflammatory mediators. TYK2 inhibitors, such as deucravacitinib, selectively target the regulatory pseudokinase domain of TYK2, which mediates IL-23, IL-12, and type I interferon signaling. This selective mechanism reduces off-target inhibition of other JAK family members, potentially improving the safety profile compared to pan-JAK inhibitors.

Clinical and mechanistic studies show that TYK2 inhibition attenuates IL-23/Th17 signaling in psoriasis, decreasing keratinocyte hyperproliferation and inflammatory chemokine production. Phase II and III trials demonstrate that selective TYK2 inhibition achieves high PASI75–100 responses while minimizing broad immunosuppressive effects [32,33].

Efficacy

- **Deucravacitinib (oral, selective TYK2 inhibitor)** has shown robust efficacy in moderate-to-severe plaque psoriasis, achieving PASI75 rates >50% at week 16 and PASI90 rates approaching 30–40% in phase III trials.
- **Zasocitinib (TYK2 inhibitor)** and **AC-201 (TYK2/JAK1 inhibitor)** also report high response rates in phase II studies, with PASI75 achieved in 48–74% of patients depending on dose and trial arm.
- Combination with topical therapy or phototherapy further enhances outcomes in extensive disease.

Safety

Selective TYK2 inhibitors generally exhibit mild to moderate adverse events, such as nasopharyngitis or mild laboratory abnormalities.

Serious adverse events remain rare but may include infections or transient laboratory changes. Compared to pan-JAK inhibitors, TYK2 selectivity reduces risks of cytopenias, thromboembolism, and cardiovascular complications. Mohammed et al. (2025) conducted a meta-analysis confirming that selective TYK2 inhibitors provide efficacy comparable to biologics, with a favorable safety profile. Zasocitinib trials reported TEAEs in 53–62% of patients, mostly mild, without treatment discontinuations. These data highlight the potential of TYK2 inhibitors as oral alternatives for moderate-to-severe plaque psoriasis [2,5].

Combination therapy: Phototherapy or topical agents may be used to enhance efficacy.

Regulatory considerations: Deucravacitinib has FDA approval for adults with moderate-to-severe plaque psoriasis. Other TYK2 inhibitors are under trial or pending approval.

Long-term safety: Ongoing studies are evaluating ≥ 1 -year efficacy and safety; real-world data for extended use remain limited.

Clinical reviews stress careful patient selection and monitoring due to immunomodulatory effects. Oral TYK2 inhibitors offer convenience and strong efficacy, but clinicians must balance benefits against potential long-term risks [29]. Selective inhibition of JAK/STAT signaling, particularly via TYK2 inhibitors, represents a promising therapeutic advance in moderate-to-severe plaque psoriasis. Oral agents like deucravacitinib achieve high PASI response rates with a manageable safety profile. Future studies will clarify long-term outcomes, optimal patient selection, and potential combination strategies. TYK2 inhibitors may emerge as viable alternatives or complements to injectable biologics, especially for patients seeking oral therapy.

Alopecia areata

Alopecia areata is a condition that results in non-scarring hair loss that can be either partial or complete. Evidence suggests AA to be autoimmune in nature via a loss of immune privilege. There is also evidence of associated T cells attacking growth at the level of the hair follicle. The prevalence of this condition is approximately 1.7 to 2.1%.[2] Baricitinib and ritlecitinib are JAK inhibitors FDA-approved for the treatment of AA. Baricitinib was studied in two randomized, double-blind, placebo-controlled trials. Patients in these trials had 50% scalp hair loss or more determined using the Severity of Alopecia Tool (SALT) for at least 6 months. The results supported both safe and effective outcomes and baricitinib gained FDA approval in June 2022. The measurement for efficacy in both trials was primarily the proportion of patients who reached at least 80% scalp hair coverage at week 36.[2]

Ritlecitinib was recently approved by the FDA in June 2023 for the treatment of severe alopecia areata in patients 12 years of age and older. In a 2 b-3 trial, patients with at least 50% or more scalp hair loss according to the Severity of Alopecia Tool (SALT) were enrolled and evaluated with the endpoint goal being a SALT score of 20 or less by week 24 of treatment. After 6 months, 3% of patients treated had 80% or more scalp hair coverage when compared to 1.6% with placebo. The efficacy as well as safety was consistent between adolescents (12–17 years of age) and adults (18 years of age and older).[35]

A study conducted by Egeberg *et al.*[36] concluded that baricitinib has the most efficacy in the treatment of AA based on the evidence available when compared to other approved treatments for severe AA. Some of these other treatments included topical immunotherapy, cyclosporine A, methotrexate, and azathioprine. Other JAK inhibitors continue to be studied for the treatment of alopecia areata, including abrocitinib and upadacitinib. They each have been found to be efficacious compared to placebo but have yet to be approved by the FDA and require further investigation.[35]

Adverse effects and monitoring

It is important to understand the safety profile of JAK inhibitors as a provider to educate patients regarding the risks and benefits. The class of JAK inhibitors carries a box warning for malignancy, infections, major adverse cardiovascular events, thrombosis, and mortality. This label was placed by the FDA due to a randomized controlled trial of oral tofacitinib versus TNF-alpha in rheumatoid arthritis. All participants were 50 years of age or older and had to have at least one cardiovascular risk factor.[37] The endpoint for the study was identifying adverse cardiac events and malignancies. The findings of the study were applied to all JAK inhibitors, regardless

of emerging data, and applied to drugs still under development. The risks on the label are not equal across all JAK inhibitor treatment regimens and some of the risks have been shown to be dose-dependent.[38] Topical JAK inhibitors such as ruxolitinib do not carry the box warning and systemic absorption is deemed minimal. Taking into consideration the percent concentration and body surface area, the topical is being applied to allow an open discussion with patients regarding risks and benefits.

Educating patients regarding the context of the box warning and data relevant to each individual medication rather than as a collective group is crucial to patient understanding, compliance, and outcomes.[38] Safety data continues to grow for patients with atopic dermatitis and other skin conditions, but overall safety profiles continue to be reassuring.[39] The need for monitoring and close follow-up should be discussed with the patient, keeping in mind the overarching context regarding the risks and benefits that are relevant to that unique patient and medication.[39] The TYK2 inhibitor deucravacitinib does not carry a box warning. Careful consideration is advised in patients with renal and hepatic impairment as well as pregnant women, women of reproductive age, and patients who are breastfeeding. JAK and TYK2 inhibitors are not recommended to be used in combination with other JAK inhibitors, cyclosporine, biologic immunomodulators, or other immunosuppressants. Commonly observed side effects of oral JAK inhibitors include acne, upper respiratory tract infections, headaches, and elevated creatinine phosphokinase levels. Additional adverse reactions such as hypertension and abdominal pain are listed in association with higher doses of certain JAK inhibitors such as abrocitinib.[40]

Topical JAK inhibitors such as ruxolitinib are safe and tolerated well. Most adverse effects identified in clinical trials have been categorized as mild and not related to the medication itself. When using ruxolitinib to treat atopic dermatitis, the most common adverse reactions included nasopharyngitis, ear infections, and urticaria among others.[41] In non-segmental vitiligo treatment, acne, headaches, and urinary tract infections are among some of the most common adverse effects.[42]

Conclusion

The increasing integration of JAK and TYK2 inhibitors into dermatologic care underscores the necessity for a comprehensive understanding of their pharmacologic profiles, approved indications, and evidence-based monitoring strategies among primary care providers. Emerging research continues to reveal novel therapeutic applications across a spectrum of inflammatory and autoimmune skin conditions, suggesting the potential for expanded regulatory approvals in the near future. Facilitating informed discussions with patients regarding both safety data and potential laboratory or systemic effects enhances interdisciplinary collaboration between

dermatologists and primary care clinicians, ultimately optimizing treatment outcomes. As the clinical experience with JAK and TYK2 inhibitors grows, ongoing investigation into their long-term safety, mechanistic nuances, and the development of next-generation agents will remain pivotal in shaping future dermatologic practice.

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