Review Article

JAK 1-3 inhibitors and TYK-2 inhibitors in dermatology: Practical pearls for the primary care physician

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Abstract

Guidelines for primary care clinicians on monitoring and safety guidelines regarding Janus kinase and tyrosine kinase 2 inhibitors in the treatment of inflammatory skin conditions are often unclear. This review aims to provide the primary care physician with a review of clinically relevant and updated information regarding the monitoring and overall profile of these medications. To do so, a systematic review was conducted using the PubMed database and relevant Food and Drug Administration (FDA) approved drug inserts from manufacturers. Janus kinase and tyrosine kinase 2 inhibitors have recently gained FDA approval for the treatment of several inflammatory skin conditions including atopic dermatitis, plaque psoriasis, alopecia areata, and vitiligo. There is a known box warning associated with the Janus kinase inhibitors that create the need for monitoring and close follow-up while patients are undergoing these treatments. Although these medications are often prescribed by specialists, as their use becomes more prevalent and therapies continue to gain approval for the treatment of these commonly encountered conditions, it is important for the primary physician to be updated and aware of the current monitoring guidelines and safety profile for this class of medication. Both Janus kinase inhibitors and tyrosine kinase 2 inhibitors display significant efficacy in the treatment of their approved conditions and research continues to move forward with the approval of more medications from these classes.

Keywords: Alopecia areata, atopic, dermatitis, Janus Kinase inhibitors, psoriasis, tyrosine-protein kinase inhibitors, vitiligo

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.[1] 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.[2]

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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.[3] 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

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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.

Methods

A systematic review of the published literature was conducted. The literature search included PubMed databases as well as drug labels from the manufacturers. Search terms included "Janus kinase inhibitors," OR "tyrosine kinase inhibitors. Articles relevant to indications and monitoring guidelines were only used if published in 2018 or sooner. Exclusion criteria included scientific posters, abstracts, and studies involving non-human subjects.

The Janus kinase signaling pathway

The JAK/STAT pathway holds an important role in immune system regulation and development. Cytokines play a crucial part in autoimmune pathologies as well as the body's immune response. Janus kinases mediate the signal transduction of many of those cytokines via the JAK/STAT pathway. The process begins once a specific transmembrane receptor binds to a ligand. The receptor then dimerizes and phosphorylates. This allows the associated JAK proteins to be drawn in and auto-phosphorylated as well.[3] This phosphorylation activates the JAK proteins, leading to increased kinase activity. The four JAK proteins in humans are JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). The activated JAK proteins phosphorylate associated tyrosine residues, which allows a site for the STAT proteins to connect. These STAT proteins are phosphorylated, dimerized, and then translocated to the nucleus. In the nucleus, the STAT proteins can begin the induction of transcription of target genes resulting in the activation of both innate and acquired immunity.[2]

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.[4] Additionally, TYK2 inhibitors are orthosteric inhibitors that impede adenosine triphosphate (ATP) binding to the JH1 catalytic domain and are not entirely selective.[5]

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.[5] 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.[6] 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.

Atopic dermatitis

Atopic dermatitis is an inflammatory skin condition that is chronic in nature and usually first observed in childhood. The prevalence of AD can be upward of 20% in children and 10% in adults depending on geographics.[15] AD clinically presents as eczematous lesions that decrease the quality of life through a variety of effects including pruritus and an increased risk for developing depression.[16] Cytokines interleukin (IL)-4, IL-13, and IL-31 play a significant role in the pathogenesis of AD via the JAK-STAT pathway.[17]

Currently, abrocitinib and upadacitinib are systemic JAK inhibitor treatments FDA-approved for AD. Upadacitinib gained

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 (Olumiant®)	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 JAK1, 2	Capsule Extended-release tablet	Severe alopecia areata in adults and adolescents 12 years of age and older[11] Psoriatic arthritis in adults and children 2 years of age and older[12]
Tofacitinib (Xeljanz®) Upadacitinib (Rinvoq®)	JAK 1	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-y, IL-6, IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 JAK 2: IL-23, IL-12, IFN-y, 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-y, IL-6, IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 Immune system, metabolic activity, lipid metabolism
Baracitinib (Olumiant®)	JAK 1: Type I IFN, IFN-y, IL-6, IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 JAK 2: IL-23, IL-12, IFN-y, IL-6, EPO, GH, GM-CSF, TPO, leptin, prolactin, IL-3, IL-5 Immune system, blood cell development, metabolic activity, lipid metabolism
Deucravacitinib (Sotyktu™)	TYK2: IL-23, IL-12, Type I IFN Immune system
Ritlecitinib (Litfulo®)	JAK3: IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 Immune system, metabolic activity
Tofacitinib (Xeljanz®)	JAK 1: Type I IFN, IFN-y, IL-6, IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 JAK 2: IL-23, IL-12, IFN-y, IL-6, EPO, GH, GM-CSF, TPO, leptin, prolactin, IL-3, IL-5 Immune system, blood cell development, metabolic activity, lipid metabolism
Upadacitinib (Rinvoq®)	JAK 1: Type I IFN, IFN-y, IL-6, IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 Immune system, metabolic activity, lipid metabolism

FDA approval in 2022. Two replicate phase 3 trials displayed improvement in EASI score, itch, and quality of life that was significant when using upadacitinib compared to the placebo ($P < 0.0001$).[18] Abrocitinib gained FDA approval in 2022, as well, after phase 3 trials demonstrated significantly improved responses in EASI and IGA scores compared to placebo.[16] Baricitinib has gained approval for AD in Europe and Japan but has yet to be approved in the US. Phase 3 findings reveal baricitinib was more effective at reaching IGA treatment success and better EASI scores versus placebo.[19]

Ruxolitinib is a topical JAK inhibitor FDA-approved in the US for AD. In results from phase 2 and 3 trials, ruxolitinib improved both pruritus and EASI in patients with moderate to severe atopic dermatitis.[15]

A meta-analysis by Sedeh *et al.*[20] concluded that upadacitinib 30 mg once daily resulted in the best outcomes compared to dupilumab, tralokinumab, and other JAK inhibitors based on EASI-50, EASI-75, and EASI-90. A study by Silverberg *et al.*[21] also found upadacitinib 30 mg to be most efficacious when compared to other systemic therapies for AD. Dupilumab, a monoclonal antibody, used in the treatment of AD was found to have the best efficacy using the endpoint EASI-50 in combination with topical corticosteroid therapy. In this same study, patients treated with abrocitinib 200 mg once daily in combination with topical corticosteroids were found to have the best outcomes for EASI-75 and EASI-90. A meta-analysis by Li *et al.*[22] found results of interest supporting better effectiveness from topical JAK inhibitors compared to systemic administration. Other topical options, such as topical corticosteroids, are found to be effective but often limited by adverse effects such as skin atrophy and skin discoloration associated with long-term use. Topical calcineurin inhibitors are safe and effective but also carry a black box warning for cancer.[22]

Psoriasis vulgaris

Psoriasis vulgaris is another common, chronic inflammatory skin disease and affects around 2% to 3% of the world population.[23] Psoriasis is known for its periods of flare-ups and remission. The pathology is known to have a genetic component as well as inheritance that is multi-genetic. The inflammatory response is driven by T cells primarily. Cytokines mediate the process, specifically tumor necrosis factor (TNF)-alpha, IL-17, and IL-23 among others.[23] By inhibiting many of these cytokines that are crucial in the pathogenesis of psoriasis, JAK inhibitors have shown themselves to be a viable treatment option for the condition.

Deucravacitinib is FDA-approved for the treatment of plaque psoriasis and works by the inhibition of TYK2. In the phase 2 study, deucravacitinib was shown to be effective compared to placebo and according to the manufacturer, a PASI75 response of 58.7% was achieved compared to 9.4% with placebo and 35.1% with apremilast in the phase 3 study.[5] Tofacitinib is an oral JAK inhibitor well known for its FDA approval in psoriatic arthritis but has not gained FDA approval for plaque psoriasis due to concerns surrounding clinical efficacy and the effects of long-term use.[23] Baracitinib continues to be studied, as well, for the use of plaque psoriasis.[24]

In a study by Zhange *et al.*, JAK inhibitors were found to have non-inferior safety compared to placebo.[25] Tofacitinib 2 mg twice daily was ranked first, followed by deucravacitinib 3 mg once daily. Studies do not indicate the superiority of JAK inhibitors when compared to other recent biologic drugs regarding efficacy. When compared to other currently used systemic therapies such as etanercept, the efficacy observed in JAK inhibitors was more efficacious.[24]

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).[25]

A study conducted by Egeberg *et al.*[26] 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.[25]

Vitiligo

Vitiligo is a chronic autoimmune disorder resulting in the depigmentation of the skin due to the destruction of melanocytes. The global prevalence varies geographically but ranges from approximately 0.5% to 2.0%. The frequency at which anti-melanocyte $CD8^{+}$T cells are in the blood has been determined to correlate with the severity of the disease. Although there are multiple theories regarding the pathogenesis of the disease, studies support an abnormal activation of innate immune cells that produce cytokines that activate auto-reactive $CD8^{+}$ T cells. Among the cytokines produced by T cells, interferon y (IFN-y) is prominent. IFN-y has been shown to play a critical role in driving vitiligo inflammation and displays dependence on JAK1-JAK2.[27]

In July 2022, ruxolitinib became the first JAK inhibitor to be FDA-approved for the treatment of vitiligo and remains the only one approved at this time.[28] The drug works by suppressing the IFK-y signaling via the JAK/STAT pathway.

Compared to traditional therapies such as systemic glucocorticoids and phototherapy, JAK inhibitors show promising data in the treatment of vitiligo; however, the use of phototherapy initially to stimulate the regeneration of melanocytes remains controversial and requires further studies.[29] Several other JAK inhibitors such as tofacitinib and baricitinib, as well as ritlecitinib, show potential but require further research before efficacy and safety can be ascertained.[27]

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.[30] 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.[31] 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.[31] Safety data continues to grow for patients with atopic dermatitis and other skin conditions, but overall safety profiles continue to be reassuring.[32] 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.[32] The TYK2 inhibitor deucravacitinib does not carry a box warning.

Monitoring and continued follow-ups are recommended when prescribing oral JAK and TYK2 inhibitors. Before starting a patient on an oral JAK inhibitor, it is recommended to obtain a complete blood count (CBC), evaluate for serious infections including tuberculosis (TB), and viral hepatitis, as well as complete all age-appropriate vaccinations. Note that live vaccines should be avoided immediately before, during, or immediately after treatment.[8] Specific baseline monitoring and follow-up recommendations vary depending on the medication, the indication, and provider discretion.

Drug interactions are important to consider when prescribing medications or monitoring the care of a patient on JAK and TYK2 inhibitors. JAK inhibitors are metabolized via the cytochrome P450 system and therefore medications that are inducers or inhibitors of the P450 system must be given careful consideration.[33]

Table 3: Suggested monitoring, drug interactions, and other considerations for JAK and TYK2 Inhibitors approved for the treatment of inflammatory skin conditions[7-13]

Medication with brand name	Suggested monitoring	Other considerations
Topical		
Ruxolitinib (Opzelura™)[7]	No routine lab monitoring[7]	For up to 20% BSA for atopic dermatitis and up to 10% BSA for non-segmental vitiligo[7] Not advised during breastfeeding[7]
Systemic		
Abrocitinib (Cibinqo™)[8]	Baseline: CBC with differential, CMP, lipids, hepatitis screening, TB, pregnancy, HIV, vaccinations[8] Follow up: CBC with differential, CMP, TB annually, lipids 4-12 weeks and annually[8]	Not for use in patients with ESRD or hepatic disease[8] Moderate renal impairment: 50 mg PO QD or 100 mg PO QD if lack of response to 50 mg[8] Do not use with antiplatelet therapies except low-dose aspirin during first 3 months of treatment[8] Breast feeding not recommended[8]
Baracitinib (Olumiant®)[9]	Baseline: CBC with differential, CMP, lipids, hepatitis screening, TB, pregnancy, HIV, vaccinations[9] Follow up: CBC with differential, CMP, TB annually, lipids at 4-12 weeks and annually[9]	Not recommended for use in patients with severe renal impairment[9] Patients with complete or nearly complete scalp loss consider treatment with 4 mg QD[9] Reduce dose to 2 mg QD when adequate response is reached in patients[9] Not advised during breastfeeding[9]
Deucravacitinib (Sotyktu™)[10]	Baseline: LFTs, hepatitis screening in patients with known or suspected liver disease, TB, pregnancy, HIV, vaccinations[10] Follow up: LFTs for patients with known or suspected liver disease around 12 weeks[10]	Not recommended for patients with severe hepatic impairment[10] No box warning[10] No dose adjustment recommended in patients with mild, moderate, or severe renal impairment, in patients with ESRD, on dialysis, or mild to moderate hepatic impairment[10] Not advised during breastfeeding[10]
Ritlecitinib (Litfulo™)[11]	Baseline: ALC and platelet counts, CBC with differential, hepatitis screening, TB, pregnancy, HIV, vaccinations[11] Follow up: CBC with differential, TB annually, CMP 4-12 weeks and annually[11]	Not recommended in patients with severe hepatic impairment[11] Not recommended during breastfeeding[11]
Tofacitinib (Xeljanz®)[12]	Baseline: CBC with differential, CMP, lipids, hepatitis screening, TB, pregnancy, HIV, vaccinations[12] Follow up: CBC with differential 4-8 weeks and repeat every 3 months, LFTs every 3-6 months, lipids 4-8 weeks and annually, TB annually[12]	Dosing adjustment needed in patients with moderate or severe renal impairment or moderate hepatic impairment[12] Not advised during breastfeeding[12]
Upadacitinib (Rinvoq®)[13]	Baseline: CBC with differential, CMP, lipids, hepatitis screening, TB, pregnancy, HIV, vaccinations[13] Follow up: CBC with differential, CMP, TB annually, lipids 4-12 weeks and annually[13]	For patients 12-65 years of age weighing at least 40 kg[13] Do not use in patients with severe hepatic impairment[13] Do not increase dosing if patient is older than 65 years of age or severe renal impairment[13] Not advised during breastfeeding[13]

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.[8]

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.[15] In non-segmental vitiligo treatment, acne, headaches, and urinary tract infections are among some of the most common adverse effects [Table 3].[28]

Conclusion

The expanding use of JAK and TYK2 inhibitors in dermatologic practice increases the importance of general understanding surrounding the profile, indications, and monitoring guidelines associated with these medications for the primary care physician. Ongoing research and novel applications of these medications continue to display new and effective uses that may result in expanding FDA approval and indications. Conversations with patients regarding safety data as well as understanding laboratory value changes and overall health implications when

prescribed these medications is a discussion beneficial to both the dermatologist and primary care physician to collaborate on providing the best care and outcomes. The safety surrounding JAK and TYK2 inhibitors as well as monitoring guidelines continues to be researched as well as new medications within these classes developed.

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Conflicts of interest

There are no conflicts of interest.

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