Systemic Janus kinase inhibitors in inflammatory dermatoses: A primer for general practitioners

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Background
General practitioners (GPs) are increasingly encountering patients treated with novel disease-modifying systemic treatments for chronic inflammatory conditions. The Janus kinase (JAK) signalling pathway has been strongly implicated as a key mediator in a broad cohort of chronic inflammatory conditions including rheumatoid arthritis, inflammatory bowel disease and, more recently, selective small molecule JAK signalling inhibitors have been used to treat inflammatory dermatoses such as atopic dermatitis and have led to promising outcomes.

Objective
This narrative review will discuss the role of JAK/signal transducers and activators of transcription (STAT) signalling in atopic dermatitis and other inflammatory skin conditions.

Discussion
A better understanding of the risks and benefits of JAK inhibitors, along with the recommended monitoring guidelines, will result in improved patient outcomes.

CELL SIGNALLING PATHWAYS amplify the response to inflammatory triggers and drive chronic inflammation by selective modulation of downstream gene expression. Of the numerous molecular pathways identified, Janus kinase (JAK) signalling has been identified as a pivotal regulator of immune homeostasis and derangements are noted in chronic systemic inflammatory states.

The JAK signalling pathway: What the general practitioner needs to know

The intercellular milieu consists of cytokines, such as interleukins (IL), which are released in response to inflammatory triggers. For example, in atopic dermatitis, some of the best studied cytokines include IL-4, IL-13, and IL-31, which bind to intracellular cytokine receptors that lack intrinsic tyrosine kinase activity. This complex relies on the JAK pathway for intracellular communication.[1–3] The JAK family includes JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). Tyrosine phosphorylation of cytokine receptors by JAKs enables attachment of key signalling proteins known as signal transducers and activators of transcription (STATs).[1] Following phosphorylation by attachment to JAKs, STATs translocate to the nucleus where they regulate gene expression of key mediators involved in inflammation.[1–3]

JAK signalling in atopic dermatitis and other inflammatory dermatoses

JAK signalling plays a central role in the pathogenesis of several inflammatory skin diseases, including psoriasis, vitiligo, hidradenitis suppurativa, alopecia areata and atopic dermatitis.[4] This is evidenced by numerous clinical trials demonstrating the efficacy of JAK inhibitors treating these conditions, including in severe cases that are refractory to conventional treatment modalities (Table 1).[5–22]

Atopic dermatitis (AD) is the most common inflammatory dermatosis that results as a complex interplay between genetic and environmental factors. Multiple mediators orchestrate the inflammatory response in acute dermatitis, clinically manifested by erythematous and exudative skin. In brief, allergen entry through the disrupted skin barrier stimulates keratinocytes to express cytokines that trigger T helper 2 (Th2) cell-mediated inflammation via interleukin release, key mediators being IL-4/IL-13. This serves as a platform to trigger an intracellular inflammatory cascade through selective activation of JAK signalling (Figure 1). Research has demonstrated that the lifetime prevalence of AD in the general

Table 1. JAK inhibitors for the treatment of inflammatory dermatoses

Condition	Aetiology	PBS-approved JAK inhibitor for severe disease not responsive to conventional treatments	Emerging JAK inhibitor treatment	Key references
Atopic dermatitis	Chronic relapsing inflammatory dermatosis associated with skin barrier disruption and atopic tendency	Upadacitinib	Abrocitinib, Baricitinib	5–9
Alopecia areata	CD8+ T cell-mediated attack on hair follicles	–	Baricitinib, Ritlecitinib	10–11
Vitiligo	CD8+ T cell-mediated attack on melanocytes	–	Ruxolitinib, Tofacitinib, Ritlecitinib, MK-6194[A]	12–14
Psoriasis	Immune-mediated chronic papulosquamous dermatosis	Deucravacitinib		15–19
Hidradenitis suppurativa	Chronic inflammatory dermatosis of follicular occlusion	–	Tofacitinib, Upadacitinib, Povorcitinib	20–22

[A]MK-6194 targets interferon-gamma, which is a cytokine that uses the JAK signalling pathway.

JAK, Janus kinase; PBS, Pharmaceutical Benefits Scheme; –, No PBS listing yet.

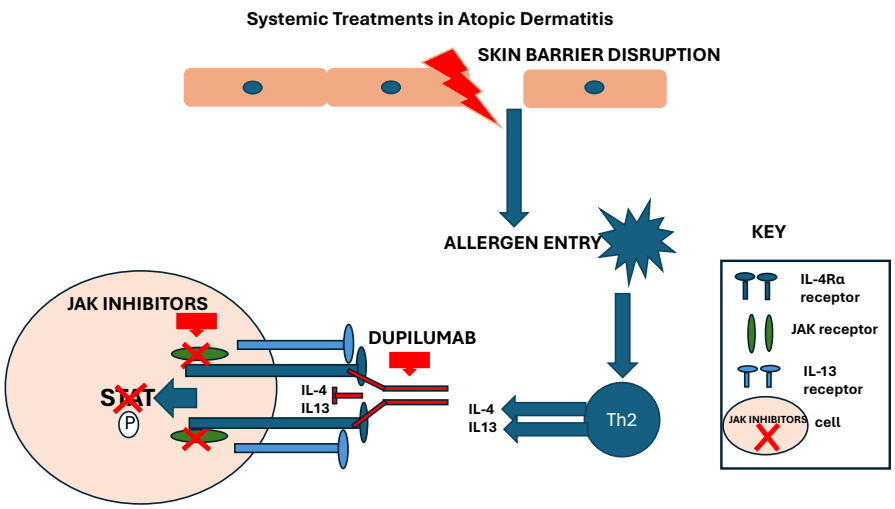

Figure 1. JAK inhibitors block intracellular signalling mediated by inflammatory triggers in atopic dermatitis by preventing JAK receptor activation and thereby STAT phosphorylation. In contrast, dupilumab acts extracellularly at the cell surface by binding to IL-4Rα, thereby inhibiting IL-4 and IL-13 signalling.

IL, interleukin; JAK, Janus kinase; STAT, signal transducers and activators of transcription; Th2, T helper 2 cell.

practice population is 16.4% and that one in five patients with AD were classified as having moderate-to-severe disease.[23] General practitioners (GPs) are therefore likely to encounter patients treated with novel systemic treatments.

Dupilumab is the first biologic agent (monoclonal antibody) that is Pharmaceutical Benefits Scheme (PBS) approved in Australia for moderate-to-severe AD and blocks IL-4/IL-13-mediated signalling.[24] Although dupilumab has been proven to be an effective treatment, a significant disadvantage of dupilumab is that it is administered by a fortnightly subcutaneous injection and is less likely to suit paediatric patients and those who are needle phobic. In addition, the high manufacturing costs involved in the development of monoclonal antibodies and the theoretical risk of neutralising antibody development are potential disadvantages.[24,25]

Selective inhibition of JAK signalling for immunomodulation is therefore an exciting prospect, given it is the key downstream mediator of inflammation.[26] JAK inhibitors are small molecule compounds that can be administered both orally and topically. Greater flexibility to withhold treatment given their shorter half-lives is also a potential advantage to patients. In addition, more selective immunosuppression also reduces the risks associated with traditional broad-spectrum systemic therapies such as oral steroids or steroid-sparing treatments.[26]

Currently, there are several JAK inhibitors that are PBS listed in Australia. Tofactinib is often referred to as a 'pan JAK inhibitor' targeting JAK 1, JAK 2 and JAK3; baricitinib targets JAK 1 and JAK 2 and upadacitinib (Rinvoq®; AbbVie, Chicago, IL, USA) is a second-generation selective JAK 1 inhibitor. Upadacitinib is PBS listed for severe rheumatoid arthritis, severe psoriatic arthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis, Crohn's disease and

ulcerative colitis; however, since 2022, it has been PBS approved for adults and children aged over 12 years who weigh over 40 kg for the treatment of moderate-to-severe atopic dermatitis, which is inadequately controlled with active topical pharmacotherapies and for whom systemic therapy is indicated.[27] More recently, deucravacitinib (Sotyktu®; Bristol Myers Squibb; Princeton, NJ, USA) targeting TYK2 was PBS listed in October 2023 for adults with severe chronic plaque psoriasis who have failed to achieve an adequate response to methotrexate.

Efficacy of JAK inhibitors

As JAK inhibitors perturb signalling mediated by a range of cytokines, they are highly effective at suppressing inflammation. The safety and efficacy of upadacitinib in the treatment of atopic dermatitis is well established from several clinical trials that showed significant improvements in the Eczema Severity Index Score, 75% improvement (EASI 75) response from baseline at week 16.[6,7] In addition, a head-to-head study comparing the efficacy of upadacitinib with dupilumab showed that upadacitinib achieved higher levels of skin clearance (EASI 90) and itch relief with a more rapid onset of action compared with dupilumab.[28]

Furthermore, deucravacitinib demonstrated superiority over both placebo and apremilast (a phosphodiesterase 4 inhibitor) across multiple efficacy end points in clinical trials for chronic plaque psoriasis with significant improvements in Psoriasis Area and Severity Index (PASI) and static Physician's Global Assessment (sPGA), and it was well tolerated in patients.[18]

How do JAK inhibitors work?

In brief, each JAK enzyme contains an adenosine triphosphate (ATP)-binding domain that mediates tyrosine phosphorylation that is critical to its function, which JAK inhibitors bind to and interact with, thus affecting their function.[29] Aside from dosing, intracellular concentration is affected by patient factors such as age, weight, liver and kidney function, and other medications.[29,30]

Recommended screening and monitoring for patients being treated with JAK inhibitors

JAK inhibitors differ in their molecular structure, specificity, efficacy and potency, and are generally well tolerated by patients overall, with the most common side effects being upper respiratory tract infection, herpes zoster infection, nasopharyngitis, nausea, headache and acne.[30] It is therefore recommended that prior to commencing treatment with JAK inhibitors, patients receive pneumococcal and Shingrix vaccinations.

JAK inhibition has been associated with haematologic abnormalities including anaemia, lymphopenia, neutropenia and thrombocytopenia, which have been noted within the first 4–8 weeks of commencement; however, in the majority of cases, these tend to normalise with long-term exposure.[30–34] Elevations in transaminases have been noted in some patients; however, this is an infrequent finding and lower risk compared with patients treated with steroid-sparing treatments such as methotrexate.[35] A dose-dependent increase in lipid levels (low-density lipoprotein [LDL]-C, high-density lipoprotein [HDL]-C) has also been noted following initiation of treatment, which warrants close monitoring in high-risk patients.[30] Alterations in creatinine kinase levels have been described; however, this has not been associated with renal impairment or rhabdomyolosis.[30–34] End-organ damage is unlikely to occur with chronic administration of JAK inhibitors in patients without pre-existing, end-organ disease.[36]

Based on these derangements, the following monitoring has been recommended for patients who are prescribed JAK inhibitors. Baseline screening recommended prior to initiation of treatment includes a full blood count, renal and hepatic function, lipid panel, as well as hepatitis B and C, HIV and tuberculosis testing.[36] Further monitoring is recommended 8–12 weeks after the initiation of treatment, with close monitoring of the lipid profile at least 12 months after treatment is established in high-risk patients, especially if derangements are noted following commencement of treatment. Further laboratory assessment is generally not required in patients treated with JAK inhibitors who do not exhibit clinically significant changes between 8 and 12 weeks.[36] Periodic review could be considered thereafter (refer to Box 1).

Serious adverse events particularly noted with pan-JAK inhibition (eg with tofacitinib) include increased cardiovascular and thromboembolic events; however, these patients were in a higher age group being treated for rheumatoid arthritis and more likely to be at risk of heart disease. Malignancies (lung cancer, lymphoma and non-melanoma skin cancer) and opportunistic infections were also noted, prompting further screening in these patients.[34]

Aside from mandating a black box warning to tofacitinib, the US Food and Drugs Administration demonstrated that risk of these serious adverse effects was higher in patients treated with tofacitinib in contrast to other disease-modifying treatments such as tumour necrosis factor (TNF)-alpha inhibitors.[34,35] Further analysis of data study demonstrated that baseline

Box 1. Recommended monitoring for patients on oral Janus kinase inhibitors[35]

Full blood count:

- Haemoglobin, lymphocytes, neutrophils, platelets

Renal function:

- Dose reduction or cessation recommended for patients with moderate-to-severe renal impairment (estimated glomerular filtration rate <30 mL/min)

Liver function:

- Transaminases

Lipid profile:

- Triglycerides, low-density lipoprotein, high-density lipoprotein

Creatine kinase

- Monitoring recommended at baseline prior to initiation of a Janus kinase inhibitor, then between 8 and 12 weeks after treatment is established. Periodic review could be considered thereafter
- Ensure pneumococcal and Shingrix immunisations are up to date

risk factors, such as a history of venous thromboembolism (VTE), hypertension or coronary artery disease, age > 65 years, smoking and hormone replacement therapy/oral contraceptive use, significantly increase the risk of VTE or adverse cardiovascular events in patients being treated with JAK inhibitors.[34–36] The Therapeutic Goods Administration in Australia has therefore recommended that JAK inhibitors should not be prescribed for chronic inflammatory conditions in people:

- with a history of cardiovascular disease (eg heart attack or stroke)
- at increased risk of cardiovascular problems (eg current or past long-time smokers)
- at increased risk of cancer
- aged 65 years and over.

unless there are no suitable alternative treatments.[36]

Non-GP specialists must therefore strongly consider the patient's baseline risk factors on a case-by-case basis when prescribing JAK inhibitors and balance the risks versus the benefits of this treatment.

Conclusion

The range of conditions amenable to treatment with topical and systemic JAK inhibitors will likely continue to expand given that dysregulated inflammation is the basis for many chronic diseases. GPs will increasingly encounter patients in everyday practice treated with novel small molecule therapies, making it essential to be well-informed about these treatments in an ever-evolving medical landscape. Defining their respective roles alongside topical and biological therapies will be important for clinical care over the years to come.

Key points

- The JAK signalling pathway is a key downstream regulator of inflammation.
- Targeted inhibition of JAK signalling is PBS approved for the treatment of inflammatory dermatoses such as severe atopic dermatitis and chronic plaque psoriasis.
- Advantages of JAK inhibition include oral mode of delivery and greater flexibility to withhold treatment.
- Serious adverse events noted with JAK inhibition can include increased risk of cardiovascular and thromboembolic events, malignancies (particularly lung cancer, lymphoma and non-melanoma skin cancer) and opportunistic infections.
- Improving the absorption and delivery of JAK inhibitors holds significant promise to further optimise patient management for the treatment of cutaneous dermatoses.

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