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Michal Bohdanowicz graduated from the University of Toronto MD/PhD program. He defended his PhD in cell biology, studying the mechanisms of phagocytosis with confocal microscopy. He completed his dermatology residency at the University of Toronto, where he served as co-Chief Dermatology resident during his final year. He is a board-certified dermatologist in both Canada and the United States. His interests include basic science and dermatopathology.

JAK-STAT PATHWAY INHIBITORS: A NEW JACKPOT FOR DERMATOLOGY

Introduction

Dermatology is experiencing an explosion of new therapies targeting the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. This pathway plays a critical role in regulating immune cells, especially the polarization of T helper cells via cytokine receptors.[1] Already, a number of dermatologic therapies target the extracellular environment, decreasing the levels of free inflammatory cytokines such as interleukin (IL)-17, IL-23, and tumour necrosis factor alpha (TNFα), or inhibiting cytokine receptors such as IL-17 receptors or IL-4 receptors. Such therapies are usually delivered as large antibody-like molecules called biologics and need to be given by injection. The new therapies, in the form of small molecules that inhibit intracellular kinases, can be given orally or topically. They are called JAK inhibitors (JAKi). For several years, they have found use in rheumatology (tofacitinib), hematologic oncology (ruxolitinib), veterinary medicine (oclacitinib) and basic science research. They are gaining increasing traction in dermatology.

Basic Science

The JAK-STAT pathway is found in many immune cells and it amplifies the signal from cytokine receptors at the surface of the cell to induce the transcription of messenger RNA in the nucleus.[2] The key protein-encoding genes in this pathway were identified using primers to amplify, from the DNA of lymphoid tissue, a conserved kinase domain that phosphorylates tyrosine residues on substrate proteins.[3,4] This conserved domain led to the discovery of 4 related protein tyrosine kinases (PTKs): JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). Members of this family, in fact, contain two kinase domains located near their C-terminal. The kinase domain closest to the C-terminal has kinase activity and phosphorylates the tyrosine residue on target proteins while the second kinase-like domain has a molecular regulation function.[5] This characteristic feature of two kinases next to each other explains why three of the proteins in the family were ultimately named after Janus, a figure in Roman mythology with two faces. The domain that involves catalytic activity is targeted by competitive JAKi, while the domain that involves molecular regulation is targeted by non-competitive or allosteric JAKi.

Further research has demonstrated that the JAK family kinases associate with the cell membrane.[6] JAK family proteins form heterodimers with other JAK family proteins, with the exception of JAK2 which can form homodimers and heterodimers.[7]

Each dimerized complex transduces signals from a unique group of receptors (**Table 1**). Ultimately, they use their kinase domain to phosphorylate and activate one of the members of the STAT family.[8] There are seven STAT proteins. Each STAT has a

JAK protein	Dimers	Cytokine	Outcome
JAK1	JAK1:JAK2	IFN-γ	• Inflammation
		IL-6, IL-11, IL-13, OSM, LIF	• T cell proliferation and survival • Wound healing
	JAK1:JAK3	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	• T cell proliferation and survival • T cell memory • B cell function
		IL-10, IL-19, IL-20, IL-22, IL-26	• Anti-inflammatory
	JAK1:TYK2	IFN-α, IFN-β	• Antiviral
JAK2	JAK2:JAK1	IFN-γ	• Inflammation
		IL-6, IL-11, IL-13, OSM, LIF	• T cell proliferation and survival • Wound healing
	JAK2:JAK2	EPO, TPO, G-CSF, GM-CSF, GH, leptin, prolactin, IL-3, IL-5	• Hematopoiesis • Growth • Anabolic metabolism
	JAK2:TYK2	IL-12, IL-23	• Psoriasis
JAK3	JAK3:JAK1	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	• T cell proliferation and survival • T cell memory • B cell function
		IL-10, IL-19, IL-20, IL-22, IL-26	• Anti-inflammatory
TYK2	TYK2:JAK1	IFN-α, IFN-β	• Antiviral
	TYK2:JAK2	IL-12, IL-23	• Psoriasis

Table 1: The four different JAK proteins, their dimers, the cytokines that signal through these dimers and their biologic outcomes. Adapted from Salas, A et al, 2020.

different function, but all are transcription factors that enter the nucleus and activate transcription after they are phosphorylated. A critical component of skin immunology, T helper cells proliferate and are polarized to a specific set of functions based on the proteins they transcribe after STAT protein activation.

In addition to dictating immune cell activation, the JAK-STAT pathway is important for receptors that bind other ligands such as prolactin, growth hormone, erythropoietin, and colony-stimulating factors. These receptors generally rely on JAK2.[7] Given the importance of JAK2 for hematopoiesis, JAKi that are non-specific or target multiple JAK proteins are finding more use in dermatologic conditions as topical formulations. Thus, JAKi can be divided into different classes that preferentially inhibit a single kinase and those that target multiple kinases (**Table 2**). This article focuses mainly on JAKi that have a dermatologic application, however there are many JAKi used in research for numerous other disease states that are beyond the scope of this review (**Table 3**).

Black box warning

Although some JAKi are still undergoing regulatory approval, all of them will likely carry a class-wide black box warning in Canada about the potential risk of serious infections, malignancies, major adverse cardiovascular events, and thrombotic events like deep vein thrombosis and pulmonary embolism.[9] This black box warning may change as more data are collected about the topical formulations, the oral selective JAK1 and TYK2 inhibitors and the impact of patient age, especially during post marketing surveillance.

Upadacitinib

Upadacitinib (Rinvoq, Abbvie Inc.) was recently approved in Canada for patients ≥12 years, weighing more than 40 kg, with moderate-to-severe atopic dermatitis. This agent is already approved in Canada for people ≥18 years of age with rheumatoid arthritis or psoriatic arthritis. In vitro, upadacitinib has selectivity for JAK1 over the other 3 JAK proteins: JAK2 (42-fold), JAK3 (133-fold) and TYK2 (194-fold).[10] It is given orally once-a-day and formulated as an extended-release tablet that contains either 15 mg or 30 mg of upadacitinib. The 15 mg dose is more widely recommended while the 30 mg dose should only be used in patients 18-64 years of age with a high atopic dermatitis burden or inadequate response to the 15 mg dose.[11]

The most common adverse reactions with upadacitinib were upper respiratory tract infections and acne.[12,13] It is also associated with shingles, cytopenia, elevated lipids, nausea and malignancy. Although not seen in the trials for atopic dermatitis, it has been associated with gastro-intestinal perforation in people taking it for rheumatoid arthritis. It is contraindicated in pregnancy, breastfeeding, hypersensitivity to upadacitinib, severe cytopenias, Child-Pugh C hepatic impairment or active infection, including local and chronic infections.

Abrocitinib

Abrocitinib (Pfizer Inc) has completed phase 3 trials in patients ≥12 years of age with moderate-to-severe atopic dermatitis.[14,15] It has gained approval in the United States, United Kingdom and Japan, but it is still under review by Canadian drug regulatory bodies. In vitro, it has selectivity for JAK1 over the other 3 JAK proteins: JAK2 (28-fold), JAK3 (> 340-fold) and TYK2 (43-fold).[16] It is given orally once-a-day and formulated as a film-coated tablet that contains either 50 mg, 100 mg, or 200 mg of abrocitinib. The key registration studies have examined the 100 mg and 200 mg formulations while the 50 mg formulation may be an option for patients with severe renal impairment (eGFR < 30 mL/min) or those taking strong inhibitors of CYP 2C[19].

Abrocitinib has reported similar adverse reactions as other oral JAKi with nausea, shingles, headache, dizziness, and acne being most common. Cytopenias, hyperlipidemia and pneumonia were rare. Venous thrombotic events, including pulmonary embolisms, occurred in the 200 mg group at a rate of 0.23 per 100 patient years but was even more rare in the 100 mg group. It is contraindicated in people with a hypersensitivity to abrocitinib, an active serious systemic infection such as tuberculosis, a severe hepatic disease or in people who are pregnant or breast-feeding.

Deucravacitinib

Deucravacitinib (Bristol-Myers Squibb Inc) has completed phase 3 trials in patients ≥18 years of age with moderate-to-severe plaque psoriasis.[17] In vitro, it has selectivity for TYK2 over the other 3 JAK proteins: JAK1 (>100-fold), JAK2 (>2000-fold), and JAK3 (>100-fold).[18] This high degree of selectivity relates to its unique method of inhibition. It binds the regulatory domain of TYK2 and inhibits the kinase domain allosterically.[19] It is given orally once-a-day and formulated as a tablet that contains 6 mg of deucravacitinib.

The most common adverse reactions reported with deucravacitinib include nasopharyngitis, upper respiratory tract infection, headache, diarrhea, and nausea.[20] Rates of malignancy, thrombotic events and serious infections were not elevated with deucravacitinib. Contraindications have not been fully identified but they will likely include hypersensitivity to deucravacitinib, pregnancy, breast-feeding and active infection.

Ritlecitinib

Ritlecitinib (Pfizer Inc.) is a covalent kinase inhibitor that inhibits JAK3, and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family. It has no activity against JAK1, JAK2 and TYK2. It has completed phase 2 trials for moderate-to-severe alopecia areata.[21]

Tofacitinib

Tofacitinib (Xeljanz, Pfizer Inc) is a JAK1 and JAK3 inhibitor that also has inhibitory activity against JAK2 (30-fold) and TYK2 (10-fold).[22] Its oral formulation is approved in Canada for rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. It has been used off-label as a treatment for recalcitrant alopecia areata[23] and case reports suggest it is effective for vitiligo when combined with phototherapy[24]. The oral formulation is associated with infections, malignancies, and thrombosis, which limit its wide-spread use.

As a 2% ointment, it has been studied as a treatment for chronic plaque psoriasis[25], mild-to-moderate atopic dermatitis[26], vitiligo (in combination with phototherapy) and alopecia areata[27]. Adverse reactions have been reported to be similar to vehicle alone, although acne and folliculitis occur more commonly.

Ruxolitinib

Ruxolitinib (Jakavi, Novartis Inc.) is a JAK1 and JAK2 inhibitor that has weaker activity against JAK3 (100-fold) and TYK2 (>10-fold) as compared to other JAKi mentioned in this review.[28] Its oral formulation is approved in Canada for the treatment of recalcitrant polycythemia vera and splenomegaly with myelofibrosis. It has been used off-label as a treatment for extensive alopecia areata[29] and it carries a black box warning about serious infections. Case reports suggest that it can cause Kaposi sarcoma.[30,31] As a 1.5% or 0.75% cream applied twice-a-day, it has been used for atopic dermatitis in people who are ≥ 12 years of age (TRuE-AD).[32] It has also been studied for vitiligo (TRuE-V), although these results are not yet published (NCT04057573). Local adverse reactions have been reported to be less common than with vehicle cream.

	Kinase Inhibitor	Selectivity	Formulation relevant to dermatology	Uses in dermatology	Pivotal trials	Efficacy	Adverse effects
Single JAK family kinase specificity	Upadacitinib	JAK1	15 mg or 30 mg (extended release tablet) once daily	Health Canada approved: atopic dermatitis ≥12 years of age	MEASURE UP 1, MEASURE UP 2, AD UP and Heads Up	EASI-75 at week 16: 30mg (76%) 15mg (65%) Placebo (15%)	Upper respiratory infections, acne, herpes simplex/ zoster, cytopenia, elevated lipids, nausea
	Abrocitinib	JAK1	50 mg, 100 mg or 200 mg (film-coated tablet) once daily	Not approved by Health Canada: Atopic dermatitis ≥12 years of age	JADE MONO-1, JADE MONO-2, JADE COMPARE and JADE REGIMEN	EASI-75 at week 12: 200mg (62%) 100mg (42%) placebo (11%)	Upper respiratory infections, acne, herpes simplex/ zoster, cytopenia, elevated lipids, nausea
	Deucravacitinib	TYK2	6 mg tablet once daily	Not approved by Health Canada: plaque psoriasis ≥18 years of age, PsA	POETYK PSO-1 and POETYK PSO-2	PASI-75 at week 16: 6mg (56%) 30mg apremilast (38%) Placebo (11%)	Nasopharyngitis, upper respiratory tract infection, headache, diarrhea, and nausea
	Ritlecitinib	JAK3 and TEC kinase	30 mg, 50 mg or 200 mg once daily	Not approved by Health Canada: Alopecia areata	No phase 3 trials	No phase 3 trails	Headache, acne, folliculitis, dermatitis, diarrhea

	Kinase Inhibitor	Selectivity	Formulation relevant to dermatology	Uses in dermatology	Pivotal trials	Efficacy	Adverse effects
Multiple JAK family kinase targets	Tofacitinib	JAK1 and JAK3 > TYK2 > JAK2	5 mg b.i.d. up to 25 mg per day	Off-label: Alopecia areata	No phase 3 trials	No phase 3 trials	Transaminitis, elevated liver enzymes
			2% ointment or cream	Not approved by Health Canada: Psoriasis, atopic dermatitis, vitiligo, alopecia areata	No phase 3 trials	No phase 3 trials	Acne, folliculitis
	Ruxolitinib	JAK1 and JAK2 > TYK2 > JAK3	20 mg b.i.d. or 25 mg/m2 BSA/day	Off-label: Alopecia areata	No phase 3 trials	No phase 3 trials	Upper respiratory infections, acne, herpes simplex/ zoster, cytopenia, elevated lipids, nausea
			0.75% or 1.5% cream b.i.d.	Not approved by Health Canada: Atopic dermatitis, vitiligo aged ≥12	TRuE AD1 TRuE AD2 TRuE V1 TRuE V2	EASI-75 at week 8: 0.75% cream (54%) 1.5% cream (62%) Vehicle (20%)	Nasopharyngitis, Upper respiratory tract infection
	Baricitinib	JAK1 and JAK2 > TYK2 > JAK3	2 mg, 4 mg	Off-label: Atopic dermatitis aged ≥18, alopecia areata	BREEZE-AD5 for atopic dermatitis, only phase 2 for alopecia areata	EASI-75 at week 16: 2mg (30%) Placebo (8%) SALT-20 at week 36: 2mg (33%) 4mg (52%) Placebo (4%)	Upper respiratory infections, acne, herpes simplex/ zoster, cytopenia, elevated lipids, nausea
	Delgocitinib	pan-JAK	0.25% or 0.5% ointment b.i.d.	Not approved by Health Canada: Atopic dermatitis aged ≥2	Phase 3 studies completed	mEASI-75 at week 4: 0.5% ointment (26%) vehicle (6%)	Nasopharyngitis, eczema herpeticum, folliculitis, acne, skin papilloma
	Brepocitinib	JAK1 and TYK2	30 mg or 60 mg once daily	Not approved by Health Canada: Alopecia areata	No phase 3 trials	No phase 3 trials	Rhabdomyolysis, upper respiratory traction infection, acne, abdominal pain, oropharyngeal pain

*Efficacy averaged from monotherapy trials of a single agent if more than one trial exists. Note that efficacy cannot be compared across different agents given differences in trial design and study populations.

Table 2: Different JAK family kinase inhibitors, their selectivity, formulations, uses and pivotal trials.

Kinase Inhibitor	Target	Notes
Filgotinib	JAK1	Approved for RA in EU and Japan but stopped clinical trials due to concerns of testicular cancer raised by the FDA
Itacitinib	JAK1	Under investigation for graft-versus-host disease; phase II for psoriasis and rheumatoid arthritis
Oclacitinib	JAK1	Used in veterinary medicine to treat pruritus in dogs
Solcitinib	JAK1	Discontinued development due to interaction with statins
Momelotinib	JAK1, JAK2, ACVR1	Under investigation for myelofibrosis
Fedratinib	JAK2	Approved by Health Canada for myelofibrosis
Gandotinib	JAK2, STAT3	Under investigation for myeloproliferative neoplasms due to JAK2 V617F mutation
Pacritinib	JAK2, FLT3, IRAK1, and CFS1R	Under investigation for myelofibrosis
Decernotinib	JAK3	Investigated for rheumatoid arthritis and graft-versus-host disease but development was terminated
Peficitinib	Pan-JAK	Approved in Japan as an oral treatment for rheumatoid arthritis

Table 3: Other JAK inhibitor medications that are currently used for non-dermatologic conditions or basic science.

Baricitinib

Baricitinib (Olumiant, Eli Lilly and Company) is a JAK1 and JAK2 inhibitor that has weaker activity against JAK3 (70-fold) and TYK2 (10-fold) as compared to other JAKi mentioned in this review.[33] Its oral formulation (2 mg tablet) is approved in Canada as a treatment for rheumatoid arthritis when combined with methotrexate. It has been studied in adults with moderate-to-severe atopic dermatitis (BREEZE-AD5 and AD7)[34] and adults with severe alopecia areata[35].

Adverse events include upper respiratory tract infections, nasopharyngitis, and folliculitis. It carries a black box warning for serious infections, malignancies and thrombosis and is contraindicated in people who are pregnant, hypersensitive to baricitinib or actively infected.

Delgocitinib

Delgocitinib (LEO Pharma and Japan Tobacco) is a pan-JAKi: JAK1 (1-fold), JAK2 (1-fold), JAK3 (4-fold) and TYK2 (19-fold).[36] Topical formulations of 0.25% or 0.5% delgocitinib ointment are under investigation in Japan for adults and children aged ≥ 2 years of age with mild-to-moderate atopic dermatitis.[37,38] Adverse events have been reported to include eczema herpeticum, nasopharyngitis, folliculitis, acne and skin papilloma.

Brepocitinib

Brepocitinib (Pfizer Inc.) is a TYK2 and JAK1 inhibitor.[21] Early studies are being completed for plaque psoriasis, alopecia areata and cicatricial alopecia.

Conclusion and future directions

JAKi are finding increasing use in the dermatologic armamentarium. They are becoming valuable oral and topical treatments for immunological skin conditions such as atopic dermatitis, alopecia areata and psoriasis and may expand their use to other immune-mediated skin diseases such as graft-versus-host disease, cutaneous lupus, and dermatomyositis. Given the expansion of molecular libraries and rational designs from inhibitor-protein crystallography, JAKi can be tailored to target a specific JAK protein via a variety of mechanisms such as competitively, covalently, or allosterically.

In addition to modulating the immune system, JAKi are anti-proliferative.[39] This property has not been fully employed in dermatology, likely because the immune system is important in preventing malignancies and some JAKi have received a black box warning from regulators that includes the potential to induce malignancy. Nevertheless, JAKi have anti-proliferative effects on melanoma[40] and skin lymphomas[41] in vitro and it is unknown whether these findings translate into improved outcomes if studied in model organisms or even patients. In fact, melanomas that acquire resistance to immunotherapy show loss-of-function mutations in the JAK-STAT pathway.[42] The application of JAKi in dermatology is still in its nascent stages and there are a number of clinically relevant uses yet to be discovered.

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