Tyrosine kinase 2 and Janus kinase–signal transducer and activator of transcription signaling and inhibition in plaque psoriasis

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Plaque psoriasis is a common, chronic, systemic, immune-mediated inflammatory disease. The Janus kinase-signal transducer and activator of transcription pathway plays a major role in intracellular cytokine signaling in inflammatory processes involved in psoriasis. Although Janus kinase (JAK) 1-3 inhibitors have demonstrated efficacy in patients with moderate-to-severe psoriasis, safety concerns persist and no JAK inhibitor has received regulatory approval to treat psoriasis. Thus, an opportunity exists for novel oral therapies that are safe and efficacious in psoriasis. Tyrosine kinase 2 (TYK2) is a member of the JAK family of kinases and regulates signaling and functional responses downstream of the interleukin 12, interleukin 23, and type I interferon receptors. Deucravacitinib, which is an oral, selective inhibitor that binds to the regulatory domain of TYK2, and brepocitinib (PF-06700841) and PF-06826647, which are topical and oral TYK2 inhibitors, respectively, that bind to the active (adenosine triphosphate-binding) site in the catalytic domain, are in development for psoriasis. Selective, allosteric inhibition of TYK2 signaling may reduce the potential for toxicities associated with pan-JAK inhibitors. This article reviews Janus kinase-signal transducer and activator of transcription and TYK2 signaling and the efficacy and safety of JAK inhibitors in psoriasis to date, focusing specifically on TYK2 inhibitors. (J Am Acad Dermatol 2022;86:148-57.)

Key words: cytokine signaling; immune-mediated inflammatory disease; inhibition; Janus kinase-signal transducer; plaque psoriasis; TYK2.

INTRODUCTION

Plaque psoriasis, a common immune-mediated inflammatory disease (IMID), substantially impairs patients' physical health, work productivity, and quality of life while increasing health care costs.[1-10] Cytokines involved in both innate and adaptive immunity mediate the psoriatic inflammatory process.[11-14] Research spanning 2 decades established that chronic inflammation in psoriasis is largely driven by pathogenic T cells, including $CD4^+$ helper T cells (Th17), $CD8^+$ T cells (Tc17), and innate lymphoid cells, which produce interleukin (IL)-17 in response to IL-23 release by dermal mononuclear cells (eg, dendritic cells).[15] Discovery of the central role of the IL-23/Th17 cell axis in the psoriatic inflammatory process has improved our overall understanding of disease pathogenesis and contributed to the identification of new therapeutic targets for this chronic condition.

Recently, biologic agents targeting IL-23 and its main effector cytokines, IL-17A and IL-17F, have been developed for psoriasis. Treatment with biologics is generally efficacious and well tolerated; however, some patients do not respond optimally, while others experience loss of efficacy over time.[16] Additional limitations of biologics include parenteral administration (intravenous or subcutaneous), risk of immunogenicity, and treatment-related

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expenses.[16] Small-molecule drugs can be administered orally or topically, routes often associated with greater patient convenience and improved quality of life.[17] However, conventional oral therapies (eg, acitretin, cyclosporine, methotrexate) are associated with various adverse events (AEs), drug-drug interactions, and long-term toxicity that require monitoring.[17] Apremilast, a phosphodiesterase 4 inhibitor approved for moderate-to-severe psoriasis, provides limited efficacy.[18] Consequently, an opportunity exists for novel oral therapies for psoriasis that are safe and efficacious.

CAPSULE SUMMARY

- Tyrosine kinase 2 and Janus kinase-signal transducer and activator of transcription signaling mediate inflammation in plaque psoriasis.
- Selective allosteric inhibition of tyrosine kinase 2 reduces the potential for adverse events associated with Janus kinase inhibitors (eg, hematologic and lipid abnormalities).

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway is an intracellular signaling system that interacts with extracellular factors to control gene expression in several IMIDs.[16,19-21] Blocking JAK-STAT signaling with oral JAK inhibitors improves clinical outcomes in psoriasis but may be associated with treatment-related toxicities.[22-24] This article reviews JAK-STAT signaling and inhibition in psoriasis, with particular emphasis on intracellular signaling mediated by tyrosine kinase 2 (TYK2), a JAK-STAT family member, and TYK2 inhibition.

JAK-STAT SIGNALING AND INHIBITION

The JAK-STAT pathway mediates signaling downstream of receptors for type I and type II cytokines, including IL-6, IL-10, IL-12, IL-22, IL-23, and interferon (IFN)-α, IFN-β, and IFN-γ.[23,25] JAK-STAT signaling is involved in immune-specific and systemic responses, including modulation of critical processes, such as hematopoiesis, lipid metabolism, and granulopoiesis.[21,26-28]

The JAK-STAT superfamily consists of 4 intracellular tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) and 7 STAT proteins.[20] JAK1, JAK2, and TYK2 are expressed ubiquitously in various cell types, whereas JAK3 is mainly expressed in hematopoietic tissue.[29] JAK1 pairs with JAK2, JAK3, or TYK2 to transduce downstream signals mediated by cytokines, including IFN-α, IFN-γ, IL-2, IL-4, IL-6, IL-7, IL-10, and IL-15 receptors.[16,30] JAK1-deficient mice have severely compromised lymphopoiesis and insufficient response to types I and II IFNs, leading to death; JAK1 deficiency in humans has not been reported.[31]

JAK2 forms a homodimer or heterodimer with TYK2. Homodimerization mediates signal transduction downstream of IL-3 and hormone-like receptors (eg, erythropoietin, growth hormone, prolactin, thrombopoietin, leptin, and granulocyte-macrophage colony-stimulating factor). JAK2 and TYK2 heterodimers are associated with type I IFN, IL-12, and IL-23 receptors.[16,30] JAK2 is mainly associated with the induction and regulation of erythropoiesis.[32] JAK2 deletion results in thrombocytopenia and anemia in mice, whereas loss of JAK2 function has not been reported in humans.[33,34] Gain of JAK2 function, however, is associated with several myeloproliferative disorders, including polycythemia vera and essential thrombocythemia.[35] JAK3, which pairs only with JAK1 and binds to the common γ-chain cytokine receptor family, is essential for lymphocyte development.[16,36] JAK3 deficiency in humans causes a lack of T cells, natural killer cells, and functional B cells, leading to a combination of severe immunodeficiency and life-threatening infections.[16,36]

JAK-STAT signaling commences with a circulating cytokine coupling to its cognate receptor on the cell membrane. This triggers a conformational change in the receptor, which activates and recruits 2 autophosphorylated JAKs. Subsequently, phosphorylated JAKs allow STAT proteins to attach, become phosphorylated, and dimerize. Dimerized STAT proteins translocate to the cell nucleus where they modify gene transcription.[20,23]

JAK inhibitors target the active sites in JAK catalytic domains, with some being more selective than others. First-generation JAK inhibitors typically target 2 or 3 different JAKs and can provide broad therapeutic benefit; however, they may be associated with more AEs than the newer generation JAK inhibitors, which more selectively target a single JAK.[16,23]

Tofacitinib, a pan-JAK inhibitor that targets JAK1 and JAK3 primarily, was efficacious in phase 3 psoriasis trials.[37-39] The proportion of patients who achieved the co-primary endpoints—Psoriasis Area and Severity Index (PASI) 75 and Physician's Global Assessment of "clear" or "almost clear" — was greater with higher tofacitinib doses (10 mg twice daily vs 5 mg twice daily)[38] and the 10-mg twice daily regimen was noninferior to etanercept.[39]

In psoriasis and rheumatoid arthritis (RA) studies, the most common tofacitinib AEs were upper

Abbreviations used:

AE:	adverse event
IFN:	interferon
IL:	interleukin
IMID:	immune-mediated inflammatory disease
JAK:	Janus kinase
JAK-STAT:	Janus kinase-signal transducer and activator of transcription
PASI:	Psoriasis Area and Severity Index
PsA:	psoriatic arthritis
RA:	rheumatoid arthritis
SLE:	systemic lupus erythematosus
TYK2:	tyrosine kinase 2

respiratory tract infection, nasopharyngitis, diarrhea, and headache.[37] Tofacitinib was also associated with dose-dependent toxicities, including dyslipidemia (elevated high-density lipoprotein, low-density lipoprotein, and total cholesterol), infections (including herpes zoster reactivation), malignancies, anemia, leukopenia, and certain cardiovascular events (eg, pulmonary thrombosis and portal vein thrombosis).[24,25,40]

Regulatory authorities recently issued boxed warnings that tofacitinib 10 mg twice daily was associated with increased risk of pulmonary embolism and higher mortality in RA patients.[16] Tofacitinib failed to gain regulatory approval in the United States for psoriasis. Clinical development of JAK1-3 inhibitors for psoriasis has largely been abandoned because of the low therapeutic index stemming from their relative nonselectivity.[17]

Tofacitinib was approved for psoriatic arthritis (PsA). Filgotinib and upadacitinib are being evaluated as potential PsA therapies.[37,41-43] Upadacitinib, a JAK1 inhibitor with partial selectivity for JAK2, improved joint and skin symptoms as early as week 2 in phase 3 trials that used stringent composite measures of disease control, in patients with active PsA who had inadequate response to nonbiologic or biologic disease-modifying, antirheumatic drugs.[26,41,42,44] No safety signals were observed beyond those previously reported in RA.[41,42]

Filgotinib, a JAK1 inhibitor, provided higher responses at week 16 than placebo in a phase 2 trial involving patients with active PsA who had an inadequate response to or intolerance of conventional synthetic disease-modifying, antirheumatic drugs. Most AEs were mild-to-moderate and the filgotinib and placebo groups had similar treatment discontinuation rates due to AEs. The most common AEs, nasopharyngitis and headache, affected a similar proportion of patients in each group.[43] Filgotinib treatment resulted in increased hemoglobin and high-density lipoprotein cholesterol levels, decreased platelet counts, and stable natural killer cell and lymphocyte counts versus baseline. No opportunistic infections (including tuberculosis), thromboembolic events, or malignancies were reported.[43]

TYK2 SIGNALING

TYK2 mediates signaling and functional responses downstream of IL-12, IL-23, and type I IFN receptors (Fig 1).[20,21,23,26-28,45-47] The IL-12 and IL-23 signaling pathways initiate and maintain chronic inflammation in psoriasis and other IMIDs.[48-54] Genetic linkage studies have revealed an association between TYK2 mutations that impair function and protection from psoriasis.[55]

TYK2 pairs with JAK2 to mediate signal transduction pathways downstream of IL-12 and IL-23 receptors.[21,26-28] IL-12 is essential for the development of Th1 cells that release the proinflammatory cytokines (tumor necrosis factor and IFN-γ). IL-23 controls expansion and survival of Th17 cells. Cytokines derived from Th1 and Th17 cells combine to amplify keratinocyte proliferation and activation.[11,29,56] TYK2 also pairs with JAK1 to mediate signal transduction pathways downstream of type I IFN receptors.

Type I IFNs, including IFN-α and IFN-β, are potent cytokines, which are rapidly produced in large quantities by various cell types, especially plasmacytoid dendritic cells, during proinflammatory states such as viral infections.[21] Type I IFNs induce powerful antiviral mechanisms, including the myxovirus resistance pathway.[46,47] They also trigger vigorous proinflammatory effects important in psoriasis, including dendritic cell maturation and activation, polarization of Th1 and Th17 cells, reduction in regulatory T-cell function, and increased activation of B cells and associated antibody production.[21] IL-12, IL-23, and type I IFN signaling mediated by TYK2 activates STAT-dependent transcription and functional responses involved in chronic inflammation. These are distinct from responses driven by JAK1–3.[21,26-28,57,58]

Studies have established that IL-12 and IL-23 signaling requires TYK2, but the requirement for type I IFN signaling remains unclear.[59,60] IL-23 administration results in epidermal hyperplasia in *TYK2*-positive mice, but not in *TYK2*-knockout mice.[61] IL-23 induces dose-dependent IL-17 and IL-22 secretion in *TYK2*-positive lymphocytes, but not in *TYK2*-knockout lymphocytes.[61] TYK2 was also required for IL-12 and IL-23 signaling, but not IFN-α signaling, in an in vitro study of novel,

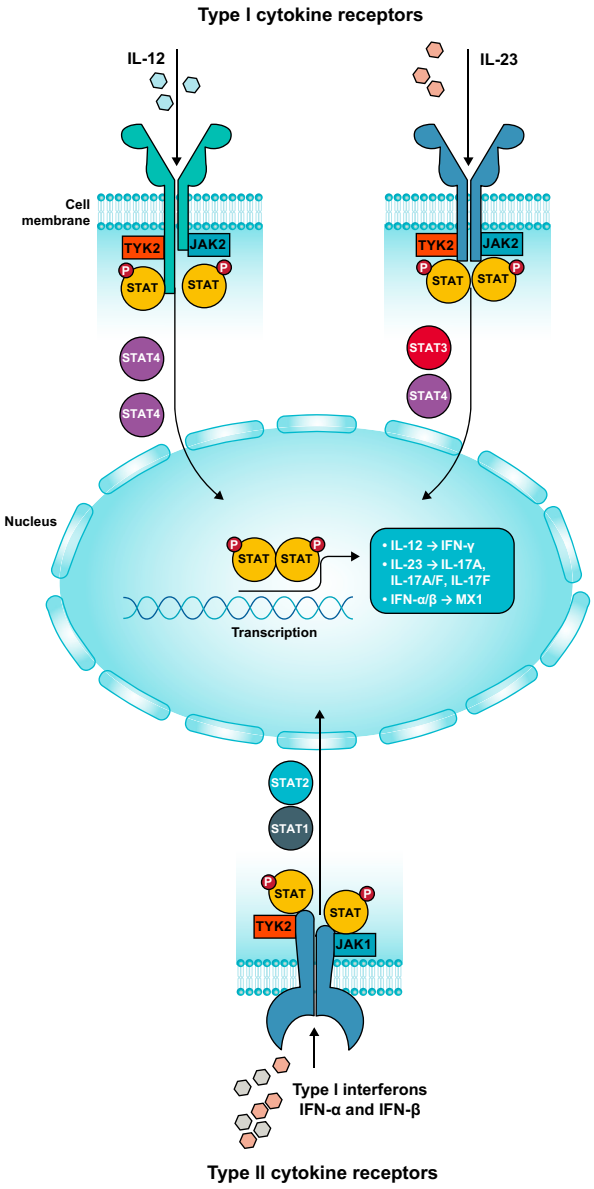

Fig 1. TYK2-mediated IL-12, IL-23, and type I IFN signaling.[20,21,23,45-47] *IFN*, Interferon; *IL*, interleukin; *JAK*, Janus kinase; *MX*, myxovirus resistance protein; *P*, phosphorylation; *STAT*, signal transducer and activator of transcription; *TYK2*, tyrosine kinase 2.

small-molecule inhibitors selective for TYK2 and JAK1.[59] However, a *TYK2*-deficient human cell line did not respond to IFN-α, suggesting that TYK2 is also essential to IFN-α signaling.[62] Finally, type I IFN signaling was reduced, but not abolished, in *TYK2*-knockout mice.[60]

TYK2 signaling is also activated by the IL-10 family of cytokines.[59] IL-10 binds to the IL-10 receptor which activates JAK1 and TYK2 and elicits anti-inflammatory effects, including the inhibition of IL-12 and class II major histocompatibility complex expression by activated dendritic cells and macrophages.[25] IL-22, a member of the IL-10 family produced in skin epithelial cells, activates JAK1 and TYK2 and is involved in maintaining epithelial integrity and stimulating chemokine production, contributing to inflammation and tissue damage.[25,59]

TYK2 INHIBITION

TYK2 inhibition is undergoing evaluation in psoriasis, PsA, inflammatory bowel disease, and systemic lupus erythematosus (SLE). A deactivating *TYK2* genetic variant, driving near-complete loss of function of IL-12, IL-23, and type I IFN signaling, is protective against autoimmunity and does not result in immunodeficiency.[63] Therefore, TYK2 inhibition may be beneficial in the management of psoriasis and PsA. Three novel TYK2 inhibitors are in development for moderate-to-severe psoriasis and PsA (Table I).[17,64,65] The available half-maximal inhibitory concentration data for the 3 TYK2 inhibitors are shown in Table II.[26,64,66]

Brepocitinib (PF-06700841)

Brepocitinib is a dual TYK2/JAK1 inhibitor with partial selectivity over JAK2, which binds to the active sites in the catalytic domains of TYK2, JAK1, and JAK2.[64] In a phase 1 trial, brepocitinib was well tolerated in healthy subjects and psoriasis patients; however, platelet and reticulocyte counts were reduced due to JAK2 inhibition.[67] In a phase 2a trial, patients treated with brepocitinib experienced significantly greater changes from baseline in PASI at week 12 (primary endpoint) compared with placebo recipients ($P < .05$). Brepocitinib was well tolerated and there were no herpes zoster infections.[68]

Biomarker analyses indicated that brepocitinib treatment reduced the expression of various inflammatory genes and cellular pathways involved in psoriasis pathogenesis.[69] Brepocitinib induced IL-17A/F inhibition more rapidly than did tofacitinib in psoriasis skin biopsies (2 weeks vs 4 weeks).[69,70] Improvements in molecular and clinical measures of psoriasis were also more rapid and complete with brepocitinib than with tofacitinib.[69,70] Although development of oral brepocitinib for psoriasis has been discontinued, Phase 2b trials will evaluate topical brepocitinib in mild-to-moderate psoriasis and oral brepocitinib in active PsA, moderate-to-severe ulcerative colitis and Crohn's disease, and SLE (Table I).

PF-06826647

PF-06826647 is an oral, dual TYK2/JAK2 inhibitor that binds to the active site in each kinase's catalytic

Table I. Clinical trials of TYK2 inhibitors in plaque psoriasis and psoriatic arthritis

Agent	MOA	Formulation	Disease	Clinical trial	Patients (N)	Study design	Primary endpoint	Projected completion
Brepocitinib[17,64]	Dual TYK2/JAK1 inhibitor Binds to the active site in the catalytic domain	Oral	PsO*	NCT02969018	212	Phase 2a, double-blinded, randomized, placebo-controlled	Change from baseline PASI at week 12: significantly higher vs placebo ($P < .05$)	Completed
		Topical	PsO†	NCT03850483	240	Phase 2b, double-blinded, randomized	Change from baseline PASI at week 12	May 2020
		Oral	PsA‡	NCT03963401	196	Phase 2b, double-blinded, randomized, placebo-controlled	ACR20 response at week 16	January 2021
PF-06826647	TYK2 inhibitor Binds to the active site in the catalytic domain	Oral	PsO*	NCT03895372	160	Phase 2, double-blinded, randomized, placebo-controlled	Change from baseline PASI 90 at week 16 Safety up to week 44	December 2020
Deucravacitinib[65]	TYK2 inhibitor Binds to the pseudokinase regulatory domain (allosteric inhibition)	Oral	PsO*	NCT02931838	267	Phase 2, double-blinded, randomized, placebo-controlled	PASI 75 at week 12: significantly higher vs placebo ($P < .001$)	Completed
				NCT03624127	600	Phase 3, double-blinded, randomized, placebo- and active-comparator controlled	sPGA 0/1 at week 16 PASI 75 at Week 16	Completed
				NCT03611751	1000	Phase 3, double-blinded, randomized, placebo- and active-comparator controlled	sPGA 0/1 at week 16 PASI 75 at week 16	Completed
				NCT04167462	180	Phase 3, double-blinded, randomized, placebo-controlled	sPGA 0/1 at week 16 PASI 75 at week 16	May 2021
				NCT03924427	80	Phase 3, open-label, single arm	sPGA 0/1 at Week 16 PASI 75 at week 16	November 2020
				NCT04036435	1680	Phase 3, open-label, long-term extension	Safety up to week 96	September 2022
			PsA‡	NCT03881059	180	Phase 2, double-blinded, randomized, placebo-controlled	ACR20 response at week 16	Completed

ACR20, American College of Rheumatology ≥20% improvement in response criteria; *JAK*, Janus kinase; *MOA*, mechanism of action; *PASI*, Psoriasis Area and Severity Index; *PASI 75*, 75% improvement from baseline PASI; *PsA*, psoriatic arthritis; *PsO*, plaque psoriasis; *sPGA*, static Physician's Global Assessment; *TYK*, tyrosine kinase.

*Moderate-to-severe disease.

†Mild-to-moderate disease.

‡Active disease.

Table II. Comparison of brepocitinib, PF-06826647, and deucravacitinib selectivity for TYK2 vs JAK1−3 in signaling and functional cellular assays[26,64,66]

		Brepocitinib		PF-06826647		Deucravacitinib
Stimulus	Signaling	IC_{50} (nM)*	IC_{50} (nM)†	IC_{50} (nM)‡	IC_{50} (nM)†	IC_{50} (nM)†
IFN-α	TYK2/JAK1	30	16	66	16	3-4
IFN-β	TYK2/JAK1	NA	NA	NA	NA	2-4
IL-23	TYK2/JAK2	120	95	112	67	9
IL-12	TYK2/JAK2	65	74-107	53	38-44	5-11
IL-2	JAK1/3	NA	23	3740	298	592
EPO	JAK2	577	99	547	39	>10,000
TPO	JAK2	NA	NA	NA	NA	>10,000

EPO, Erythropoietin; *IC_{50}*, half-maximal inhibitory concentration; *IFN*, interferon; *IL*, interleukin; *JAK*, Janus kinase; *NA*, not available; *TPO*, thrombopoietin; *TYK2*, tyrosine kinase 2.
*Values from Fensome et al.[64]
†Values from Burke et al.[26]
‡Values from Gerstenberger et al.[66]

domain.[66] In 2 phase 1, randomized, double-blind, placebo-controlled trials in healthy volunteers and patients with moderate-to-severe plaque psoriasis, PF-06826647 was well tolerated with an acceptable safety profile.[71,72]

The most common AEs in patients with plaque psoriasis were increased blood creatinine levels, increased alanine aminotransferase levels, and headache.[72] All AEs in patients treated with PF-06826647 were mild, with no serious AEs, deaths, dose reductions, or temporary discontinuations.[72] After 4 weeks of treatment, PF-06826647 effectively reduced disease activity, as measured by PASI 75, body surface area, and target plaque severity score.[72] Phase 2 trials will further evaluate the efficacy and safety of PF-06826647 in moderate-to-severe psoriasis and ulcerative colitis (Table I).

Deucravacitinib

Deucravacitinib is a novel, oral, selective TYK2 inhibitor that binds to the regulatory (pseudokinase) domain rather than to the active (adenosine triphosphate–binding) site in the catalytic domain of TYK2 where other TYK2/JAK1−3 inhibitors bind (Fig 2).[17,26,44,73,74] Binding by deucravacitinib allosterically locks the regulatory domain into an inhibitory interaction with the catalytic domain, inactivating TYK2 and preventing receptor-mediated activation and downstream signal transduction.[26]

Deucravacitinib is highly selective for TYK2 and has minimal or no activity against JAK1−3. In cell-based assays, deucravacitinib had more than 100-fold greater selectivity for TYK2 versus JAK1/3 and more than 2000-fold greater selectivity for TYK2 versus JAK2 (half-maximal inhibitory concentration data; Table II).[26,74] Dose-escalation versus target inhibition studies of deucravacitinib versus JAK1−3 inhibitors demonstrated that deucravacitinib was selective for TYK2 at clinically relevant doses.[75]

A phase 2 trial demonstrated that a significantly greater proportion of patients with moderate-to-severe psoriasis achieved PASI 75 at week 12 (primary endpoint) in the deucravacitinib 3 mg twice daily (69%), 6 mg twice daily (67%), and 12 mg once daily (75%) dosage groups compared with placebo (7%; $P < .001$).[65] The most common AEs were nasopharyngitis, headache, diarrhea, nausea, and upper respiratory tract infection.[65] No herpes zoster infections were reported and 1 patient was diagnosed with an in situ malignant melanoma 96 days after the first treatment.[65] Deucravacitinib was not associated with significant changes in hematologic parameters (lymphocyte, natural killer cell, neutrophil, and platelet counts and hemoglobin levels), serum lipid levels (high-density lipoprotein and low-density lipoprotein cholesterol), creatinine, immunoglobulins, or liver enzymes.[65,76]

The fact that dyslipidemia was not observed in deucravacitinib-treated patients is not unexpected. This AE is partially mediated via JAK1-regulated IL-6 signaling and deucravacitinib does not exert a substantial effect on IL-6 signaling in human cells.[26,30,65] These data suggest that, in contrast to JAK1−3 inhibitors, the selectivity of deucravacitinib for TYK2 reduces the potential for abnormalities in these laboratory parameters.[23,65] Biomarker analysis indicated that deucravacitinib normalized inflammatory gene expression and inhibited biologic markers of disease activity in skin biopsies, including expression of the IL-23/Th17 and type I IFN signaling pathways involved in keratinocyte activation.[77] Several phase 3 trials are evaluating

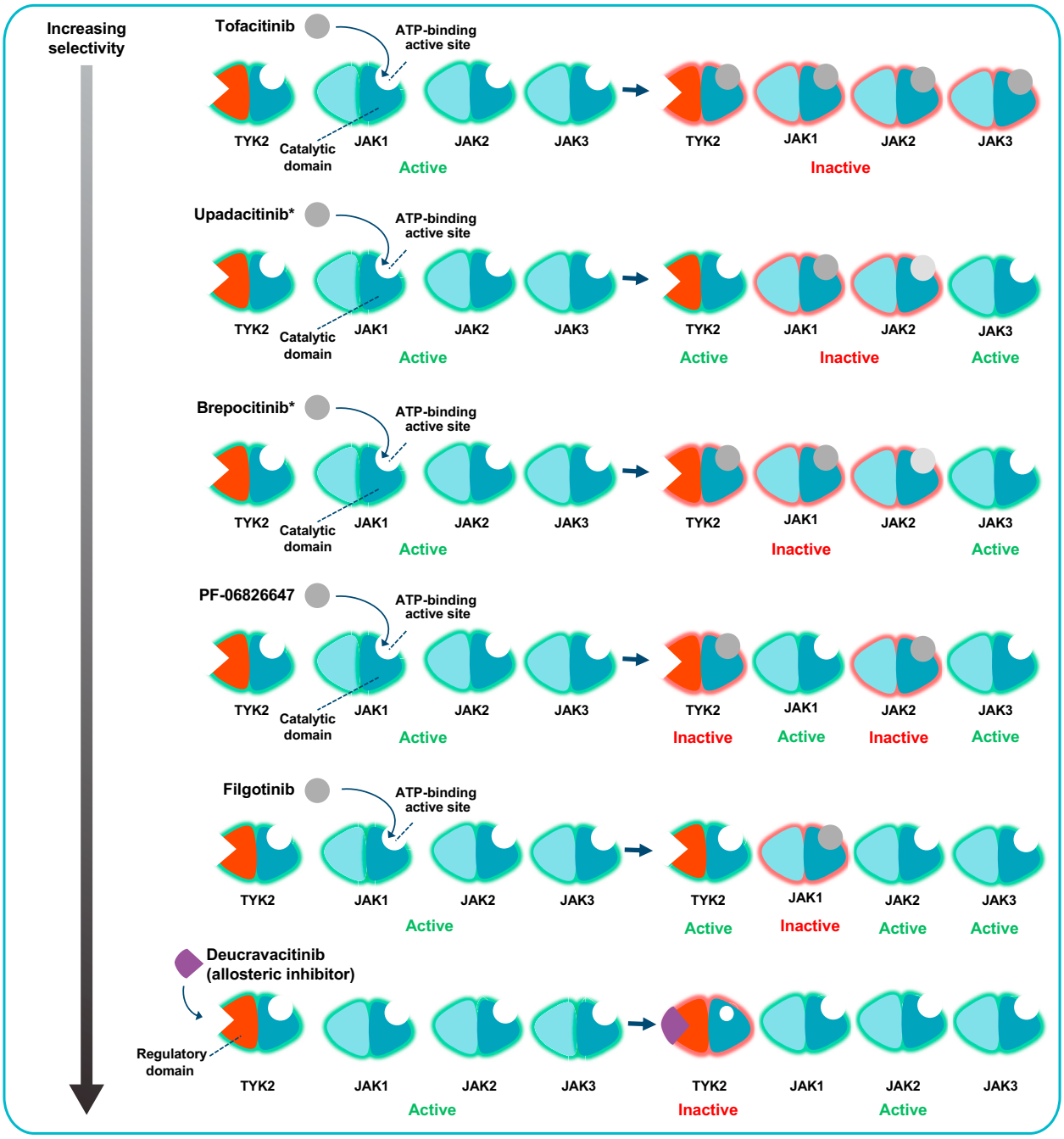

Fig 2. Comparison of selective versus nonselective inhibition of the JAK-STAT superfamily.[17,26,44] *ATP*, Adenosine triphosphate; *JAK*, Janus kinase; *STAT*, signal transducer and activator of transcription; *TYK2*, tyrosine kinase 2. *Brepocitinib and upadacitinib have partial selectivity for JAK2.

the efficacy and safety of deucravacitinib in moderate-to-severe psoriasis. Multiple phase 2 trials have been completed or are being planned to evaluate deucravacitinib in active PsA and moderate-to-severe ulcerative colitis and Crohn's disease, and SLE (Table I).

CONCLUSION

An improved understanding of the epidemiology, pathogenesis, and clinical burden of psoriasis has resulted in therapies that are efficacious for many patients. Safety and efficacy concerns persist, preventing some agents from acquiring regulatory

approval. A substantial opportunity remains for safe and efficacious oral psoriasis therapies. This is being addressed through the development of oral, small-molecule, highly bioavailable kinase inhibitors, similar to the situation in other IMIDs (eg, JAK inhibitors in RA). Available psoriasis medications have validated the concept of cytokine inhibition, with critical cytokines in psoriasis pathogenesis identified as promising therapeutic targets.

TYK2 regulates signaling and functional responses downstream of IL-12, IL-23, and type I IFN receptors, which play a central role in the pathophysiology of psoriasis. TYK2 has not been successfully targeted as yet, but laboratory and clinical evidence suggest that allosteric inhibition of TYK2 may be a viable therapeutic approach in psoriasis. Targeting the TYK2 regulatory domain rather than the active site in the catalytic domain may avoid toxicities associated with JAK1–3 inhibitors.

Three TYK2 inhibitors are in development for moderate-to-severe psoriasis and PsA. Brepocitinib and PF-06826647, which bind to the active site in the catalytic domain, are being evaluated in psoriasis and other IMIDs. Deucravacitinib is a novel, oral, selective TYK2 inhibitor in development for psoriasis, PsA, inflammatory bowel disease, and SLE. Administration of deucravacitinib to patients with moderate-to-severe psoriasis resulted in relatively high rates of clinical response, was generally well tolerated, and did not cause hematologic or lipid toxicities characteristic of JAK1–3 inhibitors. Efficacy and safety results are expected from additional trials of TYK2 inhibitors in larger populations of psoriasis patients.

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Conflicts of interest

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