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Selectivity, efficacy and safety of JAKinibs: new evidence for a still evolving story

Michael Bonelli ,[1] Andreas Kerschbaumer ,[1] Kastriot Kastrati ,[1] Kamran Ghoreschi,[2] Massimo Gadina,[3] Leonhard X Heinz ,[1] Josef S Smolen,[1] Daniel Aletaha ,[1] John O'Shea,[3] Arian Laurence[4]

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[1]Division of Rheumatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria
[2]Department of Dermatology, Venereology and Allergology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany
[3]Molecular Immunology and Inflammation Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland, USA
[4]Translational Gastroenterology Unit, Department of Haematology, University College Hospital, UCLH Hospitals NHS Trust, University of Oxford, Oxford, UK

Correspondence to
Dr Michael Bonelli, Division of Rheumatology, Medical University of Vienna Department of Medicine III, Wien, Wien, Austria;
michael.bonelli@meduniwien.ac.at

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ABSTRACT

Fundamental insight gained over the last decades led to the discovery of cytokines as pivotal drivers of inflammatory diseases such as rheumatoid arthritis, psoriasis/psoriasis arthritis, inflammatory bowel diseases, atopic dermatitis and spondylarthritis. A deeper understanding of the pro-inflammatory and anti-inflammatory effects of various cytokines has prompted new cytokine-targeting therapies, which revolutionised the treatment options in the last years for patients with inflammatory disorders. Disease-associated immune responses typically involve a complex interplay of multiple cytokines. Therefore, blockade of one single cytokine does not necessarily lead to a persistent remission in all patients with inflammatory disorders and fostered new therapeutic strategies targeting intracellular pathways shared by multiple cytokines. By inhibiting JAK-STAT signalling pathways common to families of cytokines, JAK-inhibitors (JAKinibs) have created a new paradigm for the treatment of inflammatory diseases. Multiple agents have been approved for various disorders and more are being investigated for several new indications. Second-generation selective JAKinibs have been devised with the aim to achieve an increased selectivity and a possible reduced risk of side effects. In the current review, we will summarise the current body of evidence of pan versus selective JAKinibs and the most recent insights on new side effects and indications, including COVID-19.

INTRODUCTION

Over the past decades, important insight were gained of the molecular components of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, Within this review, we will provide a brief summary of the most important findings that led to the development of inhibitors of the JAK-STAT pathway, which we will refer to as JAK-inhibitors (JAKinibs).

JAK/STAT-DEPENDENT CYTOKINES

Cytokines are structurally diverse hormones that are secreted by immune and non-immune cells. They are important for the maintenance of physiological homeostasis.[1] Cytokines bind receptors belonging to at least seven families, which subsequently activate multiple signalling pathways. In this review, we focus on a large cytokine family that binds type I/II cytokine receptors, all of which are in turn dependent on a small family of tyrosine kinases, JAK to function (figure 1).[2 3] These cytokines can be categorised into two major classes based on cytokine folding and receptor properties (box 1).

THE JAK/STAT PATHWAY

The type I/II cytokine receptors have no intrinsic catalytic activity. The receptors consist of an extracellular cytokine binding domain and a cytoplasmatic domain, which binds a combination of one to three tyrosine kinases of the JAK family. This consists of four members: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) (figure 1). In contrast with the other members, the expression of JAK3 is largely restricted to cells of the haematopoietic system.[4 5]

JAKs share conserved domain composition harbouring N-terminal FERM and SH2 domains as well as C-terminal pseudokinase and kinase domains (figure 2). JAKs are constitutively associated with the intracellular tails of receptors via the FERM and SH2 domains.[6 7] JAKs are phosphotransferases, that is, they transfer phosphate from ATP to tyrosine residues. Signalling is initiated by cytokine-induced activation of receptor-associated JAKs. Recent work revealed a role for the pseudokinase domain in dimerisation and activation of the receptor complex[7 8] leading to kinase domain autophosphorylation and trans-phosphorylation as well as phosphorylation of the receptor tails, thereby creating docking sites for latent, cytoplasmatic transcription factors termed signal transducers and activators of transcription (STATs). STATs are recruited to the receptor complex through their tyrosine-phosphate-binding SH2 domains, and become themselves phosphorylated. Thus, activated, phospho-STATs homodimerise or heterodimerise and translocate to the nucleus. Binding of dimerised STATs to DNA-regulatory elements controls transcription.[9–13] STATs bind multiple sites in the genome and regulate thousands of protein-coding genes, along with long non-coding RNAs and microRNAs. Gene transcription is also regulated by modification of the chromatin structure by STATs.[14] Thereby, JAK-STAT-dependent signalling is involved in many fundamental biological processes, including apoptosis, proliferation, migration, development and differentiation of a variety of cell types present in all organs of the body. Inhibition of one or more JAKs or STATs can lead to the inhibition of other family members. Not all the actions of type I/II cytokines in various tissues have been clarified and thus the molecular consequences/effects of JAK/STAT inhibition are currently not fully understood.

CYTOKINE-DEPENDENT ACTIVATION OF JAK/STAT PATHWAYS

The specificity of JAK/STAT-mediated signal transduction is determined by the cytokine receptor complex. Seven mammalian STAT family members have been identified (STAT1, STAT2, STAT3, STAT4, STAT5a,

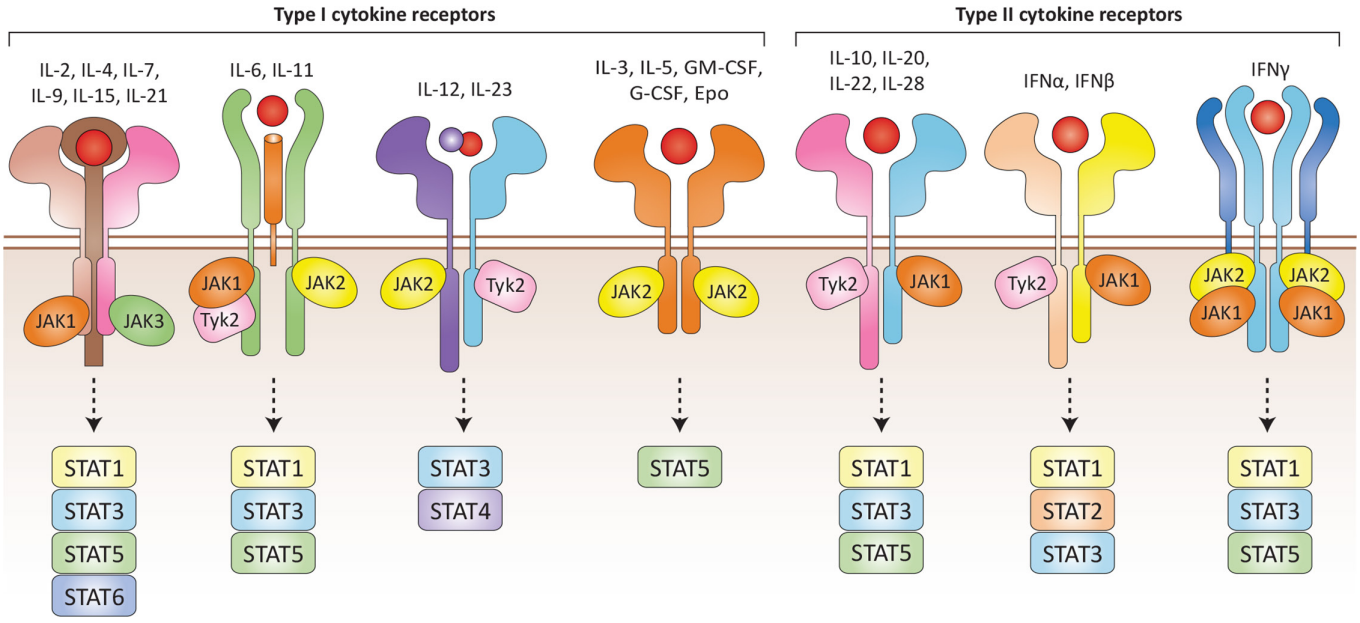

Figure 1 Type I/II cytokine receptors. Type I/II family cytokines signal through different heteromeric receptors which define the family (box 1). Members of the type I/II cytokine family include interleukins (ILs), interferons (IFNs), IFN-like cytokines, colony-stimulating factors, hormones and growth factors. The combinatorial complexity of cytokine receptor signalling is mediated by specific binding of JAK isoforms to intracellular domains and subsequent activation of STATs.

STAT5b and STAT6) that can be activated by a variety of different type I/II cytokine receptors and their associated JAKs.

The common γchain (γc) cytokines (interleukin (IL)-4, IL-2, IL-9, IL-7, IL-15 and IL-21), which activate receptor complexes incorporating the common-γ chain, signal through JAK1 and JAK3. JAK3 specifically binds to the common-γ chain and JAK1 is associated with cytokine specific α-chains and β-chains.[15] Receptor signalling leads to the phosphorylation and nuclear translocation of STAT5A/5B by all members to a variable extent.[16] IL-4 additionally activates STAT6 and IL-21 primarily activates STAT3.[16 17] Signalling in response to binding of IL-6, IL-11, IL-13, oncostatin M and leukaemia inhibitory factor to the type I receptor common gp130 chain is mediated through JAK1 and JAK2, although some data point to a role for TYK2 as well[18]; together these signals lead to a combination of STAT3 and STAT1 activation.[19] IL-12 and IL-23 activate specific receptor complexes that share the common p40 receptor chain and bind JAK2 and TYK2, which leads to the activation of STAT3 and STAT4.[20–23] Receptors for IL-3, IL-5 and granulocyte macrophage colony-stimulating factor (GM-CSF), as well as erythropoietin (EPO), thrombopoietin (TPO) and granulocyte colony-stimulating factor (G-CSF) signal solely via JAK2 and lead to STAT5 phosphorylation.[24]

The type II receptor subfamily comprises the IL-10 and interferon (IFN) cytokine families.

The latter can be divided into three subfamilies. Type I IFNs, including the many IFNα and IFNβ require JAK1 and TYK2, which leads to activation of STAT1, STAT2 and STAT4. The type II IFN, IFNγ signals through JAK1 and JAK2 that activates STAT1 and to a lesser extent STAT3.[25–27] IFNγ stimulation leads to the formation of either STAT1–STAT1 homodimers or STAT1–STAT3 heterodimers.[28] The third subfamily, the type III IFNλs (IL-28A, IL-28B and IL-29) are functionally similar to the type I IFNs.

The members of the second major, group, the IL-10 family signal through JAK1 and TYK2 and activate STAT1, STAT3 and STAT5.[29] This is similar to IFNγ but with STAT3 activated to a greater extent than STAT1 with the presence of STAT3 homodimers.

Box 1 Type I and type II cytokine family

Type I cytokines

Receptors for type I cytokines harbour a conserved WSXWS motif in their extracellular domains and bind ligands sharing a four α-helical structure.[277] Members of this receptor family can be further grouped based on shared receptor chains that combine with cytokine-specific chains to form the individual receptor complexes. The common γ-chain (γc, also known as interleukin (IL)-2 receptor γ subunit) cytokines include IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. The common β-chain cytokines include IL-3, IL-5 and granulocyte macrophage colony-stimulating factor. The third major family include cytokines that bind to the glycoprotein 130 (gp30) receptor and include IL-6, IL-11, IL-27, LIF, OSM, CT-1, CNTF, CLC and IL-31. Related to the gp130 cytokines is the dimeric cytokine family, which includes IL-12, IL-23 and IL-35. Other cytokines like erythropoietin, thrombopoietin, granulocyte colony-stimulating factor and growth hormone bind to homodimeric receptors.

Type II cytokines

The type II cytokines comprise a group of >30 signalling molecules including the interferons (IFNαs, IFNβ, IFNγ, IFNk, IFNλ2 (IL-28A), IFNλ3 (IL-28B), IFNλ1 (IL-29), IFNλ4) and IL-10-related cytokines (IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26). Type II cytokine receptors are related to type I receptors, but lack the characteristic WSXWS motif.

GENETIC EVIDENCE FOR THE SIGNIFICANCE OF THE JANUS KINASE FAMILY

Murine genetics highlight the critical role of the JAK family in mediating the actions of type I/II cytokines. This has been supported by the discovery of both loss-of-function (LOF) and gain-of-function (GOF) JAK mutations in patients (table 1).

JAK1-deficient mice die perinatally with impaired organogenesis and dwarfism in keeping with the many cytokines that rely on this kinase. However, isolated cells from these mice confirmed

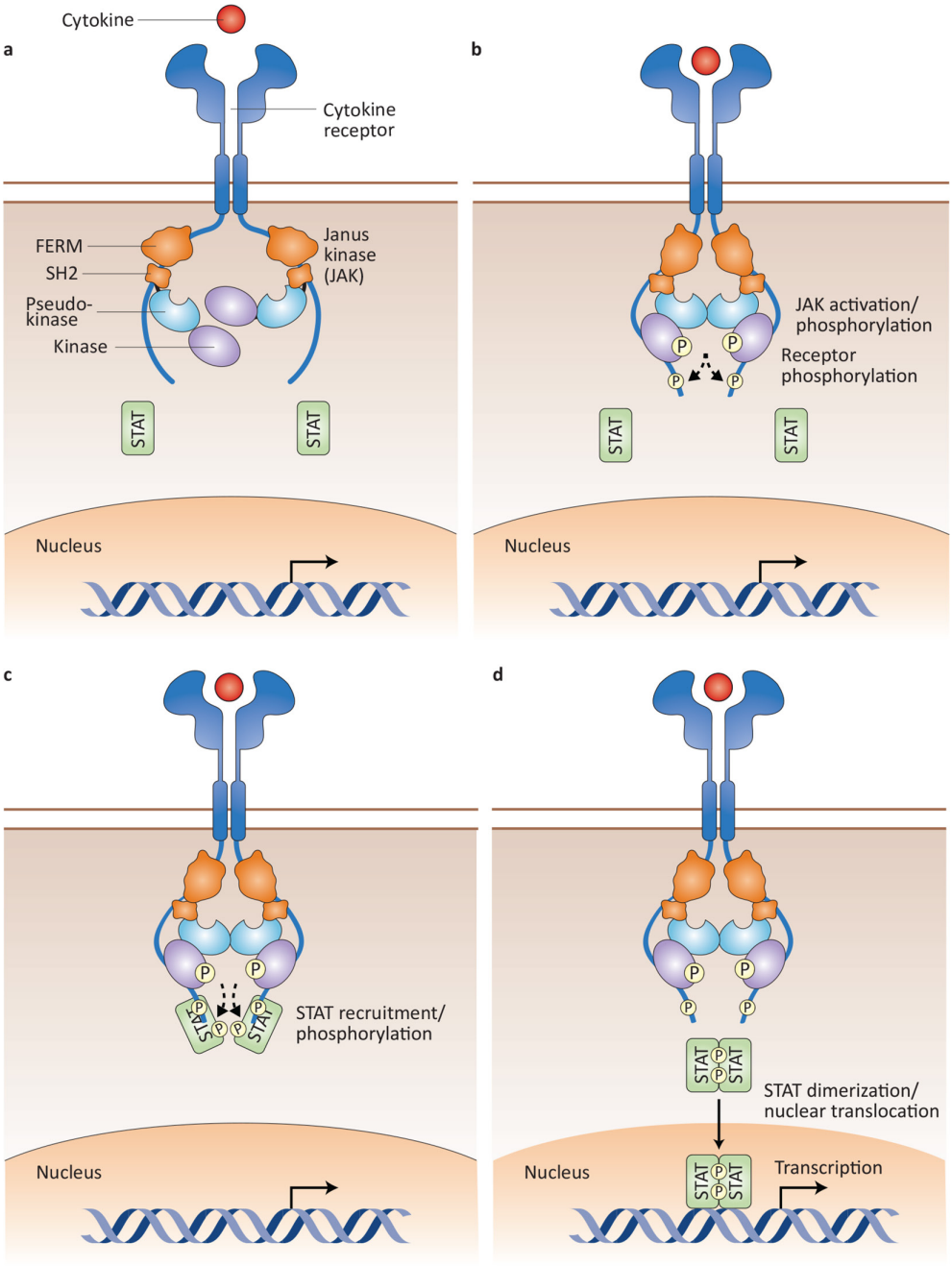

Figure 2 JAK-STAT signalling pathway. (A) Individual JAKs are constitutively associated with their specific receptors through their FERM and SH2 domains. (B) On cytokine engagement, JAKs become activated and phosphorylate each other, as well as the intracellular tails of their receptors. (C) Phosphorylation of the receptor chains generates docking sites for STATs, which can bind to the cytoplasmic domain of the receptor facilitating JAK-mediated STAT phosphorylation. (D) Phosphorylated STATs dimerise, translocate to the nucleus and bind to DNA, thereby regulating gene transcription.

an essential role of JAK1 for signalling by all class II cytokine receptors, together with the common-γ chain and gp130 cytokine families.[30] In humans JAK1 LOF mutation was shown to be associated with recurrent atypical mycobacterial infection and early onset metastatic bladder carcinoma.[31] JAK1 GOF mutations were identified in one family with autosomal dominant immune dysregulatory and hypereosinophilic syndrome.[32] Polymorphisms of JAK1 are associated with juvenile idiopathic arthritis (JIA).[33]

JAK2 has a similarly pleiotropic role including an essential role in the action of many haematopoietic growth factors. JAK2-deficient mice die in utero with bone marrow failure. There are no patients that lack JAK2 but germline JAK2 GOF and somatic mutations have been reported together with acquired JAK2 GOF mutations in patients with myeloproliferative disease.[34 35] JAK2 polymorphisms are associated with Behçet's disease.[36]

JAK3 deficiency causes a severe combined immunodeficiency in both mice and infants characterised by loss of T and natural killer (NK) cells. Curiously, B cell development is preserved in humans but not mice. Mice held in germ-free facilities are healthy but develop a slowly progressive inflammatory disease associated with splenomegaly as the few T cells that develop lack regulation. By contrast, human infants generally die of infection within the first year of life without medical intervention.[37 38]

Table 1 JAKs and STATs with associated phenotypes

JAK/STAT	Knockout mouse phenotype	Genetic links to human diseases
JAK1	Perinatally lethal	GOF: somatic mutations are seen in ALL, AML, solid-organ malignancies
JAK2	Embryonically lethal, absence of erythropoiesis	GOF: PV, PMF, ET, hypercoagulable state, haematological malignancies Polymorphisms: Behçet's disease
JAK3	Defective T and B cell maturation	LOF: T- NK- B+ severe combined immunodeficiency
TYK2	Reduced response to type I interferon and IL-12, defective STAT3 activation	LOF: primary immunodeficiency characterised by dermatitis and impaired antiviral and anti-tb immunity
STAT1	Impaired response to type I and II interferons, susceptibility to viral infections	LOF: primary immunodeficiency with viral susceptibility GOF: chronic mucocutaneous candidiasis, blood cytopenias
STAT2	Impaired response to type I interferon and susceptibility to viral infections	LOF: increased susceptibility to viral mutations
STAT3	Embryonically lethal	LOF: AD-HIES GOF: germline mutations: multisystem auto-immune diseases Somatic mutations: LGL and other T cell lymphomas Polymorphisms: Behçet's disease
STAT4	Impaired Th1 differentiation	Polymorphisms: RA, SLE, Sjögren's syndrome LOF: mycosis
STAT5a/STAT5b	Neonatally lethal: few surviving animals at birth are grossly runted and die after a few weeks	Deficiency: autoimmunity, bleeding diathesis, immunodeficiency and dwarfism Somatic mutations: LGL
STAT6	Impaired Th2 differentiation	Polymorphisms: asthma, atopy, increased IgE

AD, atopic dermatitis; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; ET, essential thrombocythemia; GOF, gain of function; HIES, hyper IgE syndrome; IL, interleukin; JAK, Janus kinase; LGL, leukaemia, large granular lymphocytic leukaemia; LOF, loss of function; PMF, primary myelofibrosis; PV, polycythemia vera; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; STAT, signal transducer and activator of transcription; Th, T helper.

TYK2-deficient mice are viable and have selective impairment of cytokine responses that include loss of IFN and IL-12/23 family cytokine responses with susceptibility to viral infections. TYK2 gene polymorphisms are linked to autoimmune diseases such as systemic lupus erythematosus (SLE) and Crohn's disease (CD), ulcerative colitis (UC), psoriasis, multiple sclerosis (MS), systemic sclerosis (SS), inflammatory myopathies, primary biliary cirrhosis and type 1 diabetes.[39] Variants of TYK2 have been shown to be catalytically impaired but to have residual signalling in response to IFNα/β, IL-6 and IL-10.[40] Variants of TYK2 are found to be associated with protection against rheumatoid arthritis (RA), SLE, inflammatory bowel diseases (IBD) and endometriosis-related infertility.[41 42] Homozygosity for the common *TYK2* P1104A allele selectively disrupts the induction of IFNγ by IL-23 and is a common monogenic aetiology of tuberculosis.[43] TYK2 deficiency in patients has been associated with a variety of clinical phenotypes. The first case included intracellular bacterial and viral infections and features of hyper IgE syndrome (HIES) such as atopic dermatitis (AD), high serum IgE levels and staphylococcal abscesses, although subsequent cases have demonstrated a phenotype characterised by suseptability to viral infections and heightened atopy.[44–46]

Mutations in STAT genes cause many immunodeficiency syndromes, and polymorphisms in these genes are associated with autoimmune diseases. Mutations in STATs can cause abnormalities in immune functions. GOF *STAT1* mutations are associated with chronic mucocutaneus candidiasis, characterised by recurrent or persistent infections of skin, nails and mucosa with *Candida* organisms.[47] Patients with inflammatory disease associated with STAT1 GOF mutations have been treated with allogeneic bone marrow transplantation with mixed success.[48 49] JAKinibs have been successfully used to correct this syndrome, but it remains to be seen if they can safely be used as a long-term treatment.[50] Dominant negative LOF STAT1 mutations with impaired IFN signalling have been characterised and present with susceptibility to viral infections.[51] *STAT2* deficiency, alongside ISG15 and ubiquitin-specific peptidase 18 (USP18) deficiencies, have been associated with severe early onset inflammation characteristic of type I interferonopathies.[52]

Dominant negative LOF *STAT3* mutations were the first reported cause of HIES. Conversely, patients with STAT3 GOF mutations have been reported and present with an early onset inflammatory disorder characterised by joint and skin inflammation. Mutations of *STAT3* have been linked to large granular lymphomas,[53] Behçet's disease,[36] CD[54] and psoriasis,[54] whereas *STAT4* polymorphisms are associated with RA and SLE.[55] STAT4 deficiencies have been associated with a novel inborn error of IL-12-dependent IFNγ immunity associated with susceptibility to paracoccidioidomycosis.[56]

Polymorphisms in *STAT6* are associated with atopy and asthma due to disturbed IL-4 signalling[57] and with recurrent mycobacterial infections including disseminated BCG disease. GOF mutations is associated with primary atopic disorders.[58] Autosomal recessive *STAT5B* mutations cause a complex syndrome characterised by dwarfism, immunodeficiency and autoimmunity and can also be associated with recurrent pneumonia and other infections.[3 4] Thus, a large body of evidence points to a critical role for JAKs and STATs in the pathogenesis of rare and common disorders of human immunity.[30]

NEGATIVE REGULATORS OF JAK/STAT SIGNALLING

JAK/STAT signalling can be both enhanced and inhibited by many accessory proteins. There are two major families of negative regulators, the protein inhibitors of activated STAT family was the first to be discovered and are consitutively expressed and bind to activated STAT dimers within the cell nucleus. By contrast, the supressors of cytokine signalling (SOCS) family are induced by STAT signalling and translocate to the JAK bound cytokine receptor complexes to generate a negative feedback loop. There are seven SOCS family members, each of which have a different repertoire of target cytokine receptors. Activation of one STAT pathway can lead to inhibiton of a second cytokine receptor JAK/STAT pathway. A group led by Rieux-Laucat has identified five families with haplo-insufficiency of SOCS1 caused by heterozygote mutations of SOCS1. Affected members present with blood cytopenias and multiorgan autoimmune diseases that phenocopy patients with STAT1 or STAT3 GOF mutations.[59] ISG15 represents an IFNα/β-induced ubiquitin-like protein and human ISG15 promotes a proviral state following IFN priming. ISG15-deficient patients do not present with any overt viral phenotype, but are highly susceptible to environmental mycobacteria and can present with autoinflammatory disease.[60 61] USP18 is a key negative regulator of type I IFN signalling by blocking the access of JAK1 to the type I IFN receptor. The absence of USP18 results

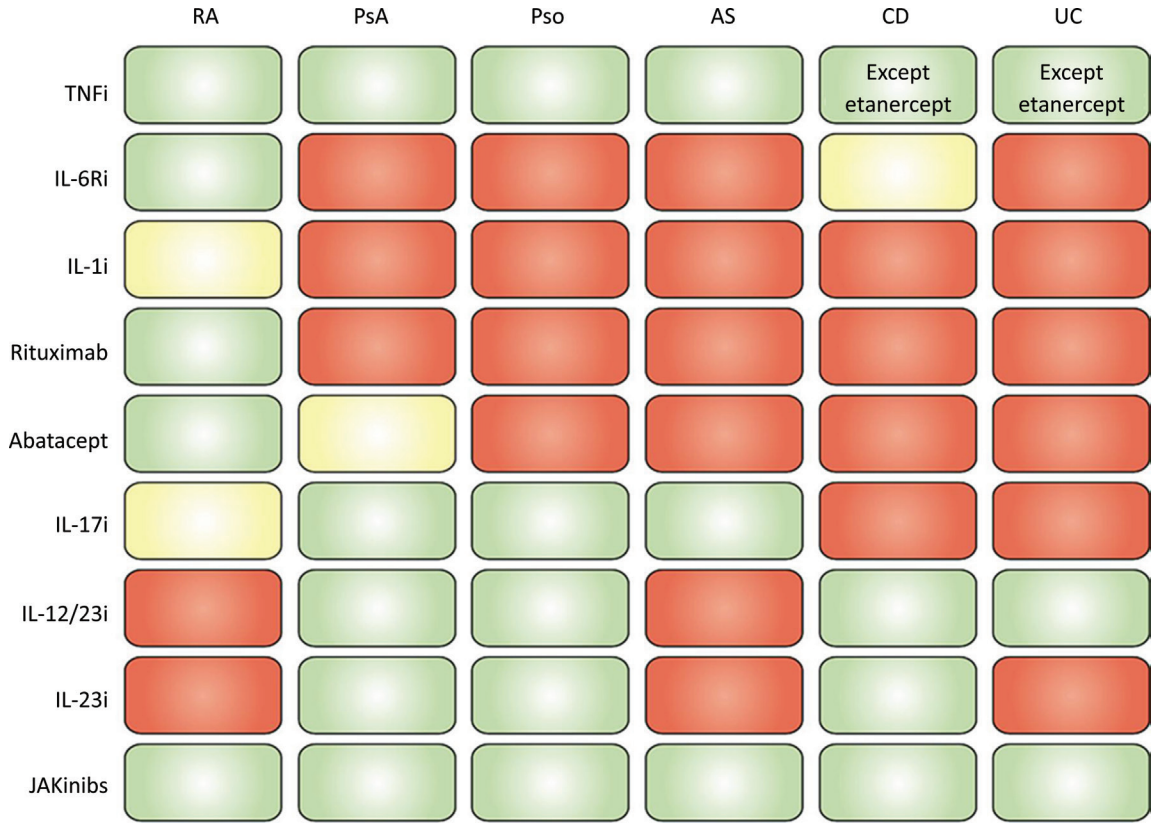

Figure 3 Efficacy of various approved agents across different therapies. Green: good efficacy; orange: low efficacy (some not approved for the respective indication); red: no efficacy (not approved for the respective indication). AS, ankylosing spondylitis; CD, Crohn's disease; i, inhibitor(s); IL, interleukin; JAKinibs, Janus kinase inhibitors; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; TNF, tumour necrosis factor; UC, ulcerative colitis.

in unmitigated IFN-mediated inflammation and is lethal during the perinatal period.[61 62]

RATIONALE AND DEVELOPMENT OF JAKINIBS

The inhibition of key cytokines by targeting their signal transduction pathways with small molecules was first articulated in 1995[63] based on genetic data. Key to the success of this approach was the realisation that it was possible to generate highly specific inhibitors of protein kinases by designing small molecules that could block the ATP docking site.

Prior to the widespread use of JAKinibs, a large number of biological disease-modifying antirheumatic drugs (bDMARDs) has been licensed in the field of rheumatology and many other areas (oncology, dermatology, gastroenterology, neurology). When focussing on rheumatic diseases, it is evident from figure 3 that most of these bDMARDs are efficacious for one or just a few diseases, while among the bDMARDs tumour necrosis factor (TNF) inhibitors are highly efficacious across all these diagnoses, but also beyond, such as IBD (figure 3) and uveitis; IL-6R inhibitors and TNF inhibitors are also approved for JIA. Despite advances in our understanding of the pathophysiology of many of these inflammatory diseases, a number of questions remain: (i) why do so many agents work selectively in one or few disorders while TNF inhibitors act so widely across diseases and (ii) why, for example in RA and psoriasis arthritis (PsA), the response rates of all these different targeted therapies are very similar. It has been hypothesised that this may be due to the pivotal role of pro-inflammatory cytokines, especially TNFα. Thus, TNFα likely represents a common shared pathway that is directly or indirectly targeted by drugs with different modes of action across different diseases.[64 65] Consistent with this theory, combinations of bDMARDs do not exhibit increased efficacy,[66 67] while the increase in serious infections attests to the interference with more than one immunological pathway. TNFα does not signal via JAKs, but uses the nuclear factor kappa B (NF-κB) and mitogen activated protein kinase (MAPK) pathways. Consequently, inhibitors of p38 MAPK, NF-κB and other signalling cascades, such as spleen tyrosine kinase (Syk) as used by Fc receptors or Bruton tyrosine kinase (BTK) as used by B cell receptors, have been a focus of clinical research. Interestingly, neither p38 nor Syk inhibition showed significant efficacy,[68 69] while phase II data for BTK inhibition showed some efficacy,[70] but the development for RA was apparently discontinued.[71] Furthermore, no compound inhibition the NF-κB pathway has yet been sufficiently studied in rheumatic diseases.

The first reported in vivo use of a JAKinibs was described for blocking allograft rejection.[72] The first generation of JAKinibs inhibits multiple JAK family members. Subsequently, more specific inhibitors have been generated (table 2). JAKinibs have been found to have a similarly broad (and maybe even broader) breadth of efficacy in various indications as the TNFα inhibitors, even though TNFα does not signal via the JAK-STAT pathway. Thus, despite more than one decade of research into a plethora of small molecules that inhibit various signal transduction pathways, only JAKinibs have hitherto provided sufficient benefit with acceptable safety aspects to make it into clinical application for patients with rheumatic diseases. It is a riddle why inhibition of other molecules does not work to a similar extent. This may be due to redundancy of pivotal pathways so that a secondary molecular path compensates if another essential one

Table 2 In vitro selectivity of common JAKinibs for the major families of type I/II cytokines

		Type I cytokine receptor				Type II cytokine receptor		
Receptor family		GP-130 family	IL-2R CGC family	IL-12/23 family	CβC family	IL-10 family	Type I IFNs	Type II IFNs
Cytokine ligands		IL-6, 11, 27, LIF, OSM	IL-2, 4, 7, 9, 15, 21	IL-12, 23	IL-3, IL-5, GM-CSF	IL-10, 19, 20, 22, 26	IFNα, β	IFNγ
Asc JAKs		JAK1, JAK2, TYK2	JAK1, JAK3	JAK2, TYK2	JAK2	JAK1, JAK2, TYK2	JAK1, TYK2	JAK1, JAK2
Downstream STATs		STAT1, 3, 5	STAT1, 3, 5, (6)	STAT3, 4	STAT5	STAT1, 3, 5	STAT1, 2, 3	STAT1, 3, 5
Inhibitors in increasing order of selectivity	Tofacitinib	+++	+++	+++	+++	+++	+++	+++
	Peficitinib	+++	+++	++	++	+++	+++	+++
	Baricitinib	+++	+++	+++	+++	+++	+++	+++
	Upadacitinib	+++	+++	++	+	+++	+++	+++
	Filgotinib	+++	+++	+	+	+++	+++	+++
	Abrocitinib	+++	+++	–	–	+++	+++	+++

The degree of inhibition is normalised against the ability of each JAKinib to inhibit JAK1 as measured by the IC_{50} value in nM.
+++=IC_{50} of the most inhibited associated JAK for a given cytokine family is lower than or equal to the IC_{50} for JAK1.
++=IC_{50} of the most inhibited associated JAK for a given cytokine family is onefold to twofold higher than the IC_{50} for JAK1.
+=IC_{50} of the most inhibited associated JAK for a given cytokine family is 2-fold to 10-fold higher than the IC_{50} for JAK1.
–=IC_{50} of the most inhibited associated JAK for a given cytokine family is >10 times higher than the IC_{50} for JAK1.
GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; JAK, Janus kinase; STAT, signal transducer and activator of transcription.

is inhibited or due to the fact that some pathways are of such crucial importance that their inhibition is afflicted with unacceptable side effects. Thus, even though JAKinibs are essential for various organ developmental steps in utero, their inhibition in adulthood does not appear to be affected with unacceptable adverse events, while still providing sufficient anti-inflammatory efficacy.

FIRST-GENERATION JAKINIBS—INDICATIONS AND THERAPEUTIC EFFECTS

Ruxolitinib was designed as a JAK2 inhibitor after the discovery of GOF JAK2 mutations in 65%–97% of patients with the common myeloproliferative diseases, primary myelofibrosis (PMF), primary polycythaemia (polycythaemia rubra vera (PRV)) and primary or essential thrombocythemia (ET).[73] It was the first Food and Drug Administration (FDA)-approved and European Medicines Agency (EMA)-approved JAKinib for the treatment of PMF. Ruxolitinib was subsequently approved for the treatment of PRV in patients with an insufficient response or intolerance to hydroxyurea. A phase II study in RA completed in 2008 (NCT00550043) remains unpublished. Ruxolitinib is effective both at reducing splenomegaly and the constitutional symptoms associated with PMF and is of benefit even in the absence of a JAK2 mutation.[74] Its success is due in part to its ability to inhibit JAK1 in addition to JAK2. Conversely, this increases the incidence of viral infections in patients on ruxolitinib. Ruxolitinib is effective in treating several inflammatory conditions and was recently FDA approved for the treatment of glucocorticoid-resistant acute and chronic graft-versus-host disease (GVHD), a major complication of allogeneic bone marrow transplantation after failure of one or two lines of systemic therapy in adult and paediatric patients 12 years and older.[75] In a recently published phase III open-label, randomised trial, treatment with ruxolitinib was superior to control therapies and associated with greater overall response, longer failure-free survival and reduction in symptoms among patients with glucocorticoid-refractory or glucocorticoid-dependent chronic GVHD.[76] Ruxolitinib is approved by the FDA for treatment of non-segmental vitiligo and for AD.

Tofacitinib (JAK1/3 and partial JAK2 inhibitor) was the first studied and FDA-approved and EMA-approved JAKinib for the treatment of patients with RA, showing efficacy across many patient populations, including patients refractory to bDMARDs,[77–79] conventional synthetic (cs)DMARDs and also patients who were methotrexate (MTX) naïve.[80] Tofacitinib was originally designed as a selective inhibitor of JAK3. Pharmacological studies revealed a blockade of JAK3 and JAK1 but JAK2 and TYK2 were also affected, although to a lesser extent. Accordingly, tofacitinib has the greatest effect on IL-6, IFNγ and common γc cytokines.[81] A head-to-head study comparing tofacitinib with adalimumab 40 mg every other week (in combination with background MTX) showed non-inferiority of the combination therapy of tofacitinib 5 mg two times per day (+MTX) and adalimumab 40 mg every other week (+MTX), but failed to demonstrate non-inferiority for tofacitinib 5 mg monotherapy.[82] Two studies confirmed the efficacy of tofacitinib in patients with PsA with insufficient response to csDMARDs or bDMARDs and led to subsequent regulatory approval of tofacitinib for PsA.[83 84] Patients with ankylosing spondylitis (AS) with insufficient response to non-steroidal anti-inflammatory drugs (NSAIDs) showed a clear dose-response relationship and significantly better outcomes compared with placebo treatment in a phase II study.[85] A phase III study (NCT03502616) has confirmed the efficacy results in patients with AS.[86] In patients with chronic plaque psoriasis, tofacitinib reduced skin disease significantly more compared with placebo treatment.[87–90] A head-to-head trial, comparing patients treated with 10 mg of tofacitinib two times per day showed non-inferiority compared with patients treated with etanercept twice weekly.[88] Tofacitinib also showed superior results compared with placebo in induction (10 mg two times per day) as well as maintenance therapy (5 mg and 10 mg two times per day) of patients with severe UC and was approved for this indication.[91] No significant difference of tofacitinib compared with placebo treatment was found when treating patients with CD.[92 93] Limited data are provided for efficacy of tofacinitib in patients with SLE. However, tofacitinib was found to be generally safe in subjects with SLE according to a phase I randomised controlled trial. Tofacitinib was safe in SLE meeting study's primary end point. As secondary end points it could be shown that tofacitinib improves cardiometabolic and immunological parameters associated with the premature atherosclerosis in SLE.[94] Ongoing trials currently investigate safety and efficacy

in patients with SLE with skin manifestations (NCT03288324, NCT03159936). The *STAT4* SLE risk allele has been associated with increased IL-12-induced IFNγ production in T cells from patients with SLE,[95] suggesting beneficial effects of JAKinibs. In a randomised, double-blind, placebo-controlled clinical trial, tofacitinib has been shown to be effective and generally safe in patients with the *STAT4* SLE risk allele.[94]

Peficitinib (pan-JAK inhibitor) was found to be modestly efficient in multicentre trials in patients with RA. However, several trials investigating Japanese patients with RA found significant improvements of disease activity and physical function with subsequent regulatory approval of peficitinib in Japan.[96–101] One phase II trial showed a significant reduction of psoriatic skin disease with peficitinib compared with placebo.[102] In patients with UC, a phase II trial failed to meet its primary end point, with only one dosage (150 mg) leading to significant improvements in remission induction after 8 weeks of treatment compared with placebo.[103] Pefecitinib is currently not considered for approval by the FDA or EMA.

Baricitinib (LY3009104) is a dual JAK1/2 inhibitor that is functionally similar to ruxolitinib and therefore suppresses IFNγ, IL-6, IL12/23, EPO and GM-CSF signalling. Baricitinib was approved for treatment of patients with RA in the 4 mg dose by the EMA and 2 mg dose by the FDA based on various studies, showing efficacy in treatment-naïve csDMARD-experienced and bDMARD-experienced patients with active disease.[104–112] In a head-to-head study, 4 mg of baricitinib (+MTX) was statistically superior to adalimumab 40 mg every other week (+MTX).[113] One phase II trial showed 8 mg and 10 mg of baricitinib to be superior to placebo treatment in patients with chronic plaque psoriasis.[114] In patients with moderate-to-severe AD, baricitinib significantly reduced inflammation and pruritus, as well as quality of life and skin pain and was EMA approved in December 2020.[115–117] Baricitinib has not been investigated in patients with PsA, AS, UC or CD so far. In a double-blind placebo-controlled phase II trial, baricitinib at 4 mg dose, but not the 2 mg dose, significantly improved the signs and symptoms of patients with active SLE.[118] However, based on results from two phase III trials to evaluate long-term safety and efficacy in patients with SLE (SLE-BRAVE I and II), baricitinib failed to provide clinical improvement in patients with active SLE receiving stable background therapy, with only baricitinib at daily dosage of 4 mg in the SLE-BRAVE I showing significant benefit compared with placebo. Other key end points were not met in either study. The use of corticosteroids was not restricted, potentially resulting in high placebo response rate.[119 120] Phase II trials investigate efficacy and safety in patients with Sjögren's syndrome (NCT05016297) and relapsing giant cell arteritis (NCT03026504). Baricitinib has recently completed phase III trials in the treatment of alopecia arreata (AA) (NCT03579749) with patients attaining a minimum of 80% of scalp recovery after 24 weeks at the 4 mg dose.[121] Consequently, the drug has been approved for this indication.

NEXT-GENERATION JAKINIBS—INDICATIONS AND THERAPEUTIC EFFECTS

The side effects of JAKinibs are both predictable and perplexing, but to some degree can be attributed to their lack of selectivity. Tofacitinib was designed as a selective JAK3 inhibitor, yet its inhibition of JAK2 contributes to the unwanted side effects of anaemia and neutropenia. Conversely, the JAK2 inhibitor, ruxolitinib, designed to inhibit bone marrow overproduction of myeloid cells, inhibits JAK1 that will contribute to the observed increased incidence of viral infections. To address this, a second generation of inhibitors that could specifically inhibit individual JAKs were developed and investigated in a several clinical trials (figure 4). However, their success has been mixed and several agents were dropped after failing in clinical trials.

Upadacitinib (ABT 494) represents a putatively selective JAK1/2 inhibitor, which has shown consistent efficacy results for RA, PsA, AS, JIA and IBD.[122 123] Upadacitinib 15 mg once daily is EMA and FDA approved for treatment of RA, PsA, AS, UC and AD, with currently pending approval for CD.[124–131] In patients with PsA, statistical superiority of upadacitinib 15 mg once daily (+MTX) compared with adalimumab 40 mg every other week (+MTX) in MTX non-responding patients[132] was achieved. In patients with PsA with insufficient response to non-bDMARDs, upadacitinib 15 mg and 30 mg once daily were superior to placebo treatment, with upadacitinib 15 mg once daily being non-inferior to adalimumab 40 mg every other week and upadacitinib 30 mg once daily being statistically superior to adalimumab.[133] Furthermore, patients with PsA with refractory disease despite previous bDMARD therapy had significant improvement of signs and symptoms as well as physical function when treated with upadacitinib, compared with placebo.[134] Upadacitinib is approved for patients with AS by the EMA and FDA. In patients with AS with insufficient response to NSAIDs, upadacitinib 15 mg once daily was superior to placebo.[130 131] In a phase III trial, efficacy and safety was shown in patients with active AS, refractory to biological therapy.[135] Two phase II trials, investigating upadacitinib in UC demonstated that 7.5–45 mg of extended-release upadacitinib (once daily) was superior to placebo in induction of remission over 8 weeks.[136] This led to a recently completed U-ACCOMPLISH phase III study using the highest 45 mg daily dose that confirmed benefit and has led to FDA approval for this JAKinib.[137]

By contrast, in patients with CD, higher rates of clinical and endoscopic remission were observed in patients treated with 3–24 mg of upadacitinib two times per day or 24 mg once daily, but no clear dose-response could be observed regarding endoscopic remission.[138] An ongoing phase III trial currently investigates efficacy and safety of upadacitinib in patients with moderately to severely active CD who have inadequately responded to or are intolerant to biologic therapy (NCT03345836). Significant improvement of AD was observed when treating severely affected patients with AD with upadacitinib,[139–141] which led to the approval for this indication by the FDA and EMA. No trial data are currently provided for the use of upadacitinib in patients with SLE. One ongoing phase II trial addresses safety and efficacy in moderately to severely active SLE (NCT03978520). Phase III trials are ongoing to address efficacy and safety in giant-cell arteritis and Takayasu arteritis (NCT03725202, NCT04161898).

Filgotinib (GLPG0634), a designed selective JAK1 inhibitor, has demonstrated efficacy for RA and UC. Filgotinib was effective compared with placebo in the treatment of patients with bDMARD refractory RA,[142] MTX-naïve patients[143] and also in MTX-inadequate response (IR) patients.[144–146] Furthermore, in MTX-IR patients, filgotinib 200 mg (+MTX) once daily was non-inferior to adalimumab (+MTX) based on DAS28-CRP ≤3.2. In September 2020, filgotinib received the approval for treating patients with RA and insufficient response to MTX treatment via the the EMA but remains currently unapproved by the FDA. Additionally, filgotinib 200 mg showed better efficacy compared with placebo in three separate phase II studies investigating patients with PsA, AS and CD.[147–149] In a combined phase IIb/III trial, filgotinib was generally well tolerated and efficacious

Figure 4 Admission of approved selective versus non-selective JAKinibs. The label in the upper box indicates the comparator referenced with the colour code (green colour indicates significant differences; red colour indicates no significant difference; yellow indicates mixed results; blue colour indicates studies meeting non-inferiority; purple indicates no formal statistical comparison and numerically similar results. *No formal statistical comparison, numerically similar results. †Tofacitinib is currently not pursued for drug approval for plaque psoriasis. ‡8/10 mg reached statistical significance, no significance was observed for 2/4 mg versus placebo. §One trial, safety only (NCT02535689). ¶Phase II trial, no data/results published (NCT03978520). **No difference was observed in patients with small bowel CD,[158] ADA, adalimumab; ETN, etanercept; JAK, Janus Kinase; NI, non-inferiority; PLC, placebo; S, superiority; TNF(R)i, tumour necrosis factor alpha receptor inhibitor.

in inducing and maintaining clinical remission in UC.[150] Safety and efficacy of filgotinib was currently investigated in phase III trials as induction and maintenance therapy for patients with moderately to severely CD (NCT02914561), but the results remain unpublished at the time of writing this manuscript. Another phase II trial in small bowel CD (DIVERGENCE-1) did not show a statistical difference when comparing filgotinib with placebo treatment.[151]

Abrocitinib (PF-04965842) is a selective JAK1 inhibitor, which has recently been approved by the FDA for the treatment of adults living with refractory, moderate-to-severe AD. The safety and efficacy of abrocitinib was evaluated in three phase III, randomised, placebo-controlled clinical trials: JADE MONO-1 and MONO-2 evaluated the efficacy and safety of two doses of abrocitinib monotherapy with moderate-to-severe AD.[152 153] Abrocitinib showed similar responses compared with dupilumab in a head-to-head trial (JADE COMPARE) investigating adult patients with moderate-to-severe AD.[154] Patients that completed 16 weeks of treatment in JADE MONO-1 and JADE MONO-2 were invited to enrol an ongoing phase III long-term extension study (JADE EXTEND—NCT034422822) including 92 weeks of treatment with abrocitinib with or without concomitant topical corticosteroids.

Decernotinib (VX-509) is a selective JAK3 inhibitor that showed some efficacy in phase II trials for the treatment of RA. However, its use is limited by multiple drug interactions, since it is metabolised by aldehyde oxidase to a metabolite that inhibits CYP3A4, which is essential for inactivation of many common drugs. The mixture of lack of efficacy, side effects and drug interactions led to an end of further development.[155–157]

Ritlecitinib (PF-06651600) is a selective JAK3 and TEC tyrosine kinase family inhibitor, which showed promising results in small, early studies investigating the treatment of RA and AA.[158 159]

Deucravacitinib (BMS-986165) is the first compound that targets the pseudokinase domain of a JAK, namely TYK2, and therefore represents a highly selective, allosteric TYK2 inhibitor that can inhibit IL-12, IL-23 and IFN signalling. Deucravacitinib was superior to placebo and apremilast treatment in a phase III trial for the treatment of patients with moderate-to-severe psoriasis[160 161] and is approved by the FDA, while EMA approval is still pending. Results from a recently completed phase II trial show efficacy of deucravacitinib in PsA.[162 163] In a phase II randomised, double-blind, placebo-controlled trial, safety and efficacy of deucravacitinib was shown in patients with active SLE with a higher response rate for the SLE Responder Index 4 at week 32 with an acceptable safety profile.[164]

Brepocitinib (PF-06700841) targets TYK2 and JAK1 selectively and was efficacious in phase II studies in patients with chronic plaque psoriasis[165] and AA.[159]

EXPERIMENTAL EVIDENCE FOR JAKINIB SELECTIVITY

Clinically approved JAKinibs have been developed with a specific target spectrum in mind,[166] however selectivity for individual JAK isoforms in vivo is most likely relative and influenced

by multiple variables such as dose, drug metabolism and target cell spectrum. The bulk of protein kinases have been designed as competitive ATP antagonists. The first protein kinase inhibitors were able to inhibit a limited number of kinases by virtue of a gatekeeper residue that is found within the ATP binding region only when the kinase is in the inactive state.[167] This residue varies in different kinases and is both used by drug companies to generate selective inhibitors and mutated by cancer cells to escape the effect of these kinase inhibitors. All JAK family members use methionine as a gatekeeper residue posing challenges for designing highly selective JAKinibs. This can be overcome in part by the use of novel strategies such as targeting the inhibitory peudokinase domain.

Tofacitinib (CP-690,550) was originally designed as a selective JAK3 inhibitor,[72] but subsequent studies employing in vitro kinase and cellular assays have determined that this compound preferentially inhibits cytokines that signal via JAK1 and/or JAK3 over JAK2.[168 169] Its ability to inhibit JAK1 enables the drug to inhibit many inflammatory cytokines. Tofacitinib showed efficacy in mouse and rat models of arthritis and inhibited STAT1 and STAT3 signalling in vitro and both JAK1 and JAK3 signalling pathways in the collagen-induced arthritis model.[168 170–174] This wide spectrum is likely to play a role in both the efficacy and toxicity of the drug.

Ruxolitinib and baricitinib exhibits specificity for JAK1 and JAK2 over JAK3 in kinase assays and has shown efficacy in murine arthritis models.[175 176] This wide spectrum of inhibition is likely to be responsible for the unwanted immunosuppression in patients with myelofibrosis treated with ruxolitinib and the unwanted anaemia in patients with RA treated with baricitinib.

Upadacitinib and filgotinib have been described as selective inhibitors for JAK1 over other JAK isoforms. Both inhibitors showed selectivity towards JAK1 and JAK2 over JAK3 and TYK2 in pure biochemical in vitro kinase assays, but more profound selectivity for JAK1 in cellular assays.[172 177] In a rat model of arthritis, a comparative analysis of upadacitinib and tofacitinib revealed that increased selectivity of upadacitinib for JAK1 resulted in a reduced effect on reticulocyte deployment and NK cell depletion relative to its efficacy.[177] A direct comparison of IL-7-induced pSTAT5 and IL-6-induced pSTAT3 of patients treated with these drugs from a phase I trial also revealed a higher selectivity of upadacitinib for JAK1 vs JAK3.[178] In preclinical studies, filgotinib inhibited JAK1-related pathways with higher selectivity for JAK1 over JAK2 in whole blood, peripheral blood mononuclear cells (PBMCs) and in murine arthritis models.[172–174]

While different degrees of JAK isoform selectivity have been described for clinically approved drugs, it remains unclear how data derived from in vitro experiments and in vivo models reflect clinical usefulness, since little difference has been noted for efficacy or safety. Only limited studies are available that actually provide comparative functional analyses on JAKinib selectivity. A recent study compared the inhibitory effects of tofacitinib, baricitinib, upadacitinib and filgotinib on cytokine-induced STAT phosphorylation patterns in whole blood cells using clinically efficacious doses. Even though minor numerical differences in cytokine receptor inhibition were observed, the overall inhibition profiles were similar across studied JAKinibs.[179] An additional in vitro pharmacological analysis compared the inhibitory effect of tofacitinib, baricitinib, upadacitinib in PBMCs. Although distinct pharmacological profiles for JAKinibs have been observed in this study, no continuous inhibition of JAKinibs on individual cytokine signalling pathways could be detected.[179 180]

The in vivo impact of pan versus selective JAKinibs was addressed by Moodley *et al* who performed comparative immunological, transcriptomic and epigenetic profiling of ex vivo isolated murine cells. Selective cell type specific effects of JAKinibs could be described; however, globally there was a high overlap between compared compounds.[181]

Importantly, JAK selectivity as detected in vitro by using recombinant enzymes or isolated cells may not necessarily reflect the in vivo selectivity, which is likely dependent on a large inter-individual variability of pharmacokinetic and pharmacodynamic aspects, based in part on pharmacogenomic effects on drug metabolism or tissue/cell sensitivity. Since most respective receptors use JAKs as heterodimers, it is currently not possible to understand differences in selectivity if any one of the JAK1/2, JAK1/3 or JAK2/3 heterodimers are inhibited. However, since cells of the haematopoietic system use JAK2 homodimers for signal transduction, a proxy for in vivo JAK2 inhibition constitutes the occurrence of anaemia or reversal of chronic anaemia in inflammatory states. Such in vivo effects may differ from in vitro data where the complexity of an organ system or a whole organism with its genetic, epigenetic or proteomic background is missing.

In summary, current experimental data do not allow drawing a clear conclusion of the potential advantages of a higher selectivity of next-generation JAKinibs. One still needs to learn which beneficial effects and which adverse events are associated with specific JAKinib characteristics. Thus, additional comparative experimental data of pan and selective JAKinibs on ex vivo isolated cells from clinical trial participants are needed as are head-to-head comparisons of JAKinibs with presumed differences in selectivity to understand the impact on safety and also efficacy.

Topical JAKinibs

Compared with systemically acting compounds, topically applied JAKinibs potentially have certain advantages. Key is a lower risk of potential side effects due to less systemic distribution when compared with oral administration. Thus, when used topically, pan-JAKinibs could be used for conditions in which systemic long-term treatment would not be an option due to safety concerns. Target areas for potential use of topical JAKinibs are similar to indications for topical glucocorticoid treatment, being the skin, the eyes, the gastrointestinal tract and the lungs. Efficient delivery of the compound to the target tissue is an essential prerequisite of topical JAKinib treatment. Most developments therefore focus on the skin, especially because the repertoire of anti-inflammatory drug classes that are in use for topical treatment of inflammatory skin diseases is limited to glucocorticoids, calcineurin inhibitors and vitamin D analogues. Here, formulations have to assure that the compound can penetrate into the skin and reach targets cells like keratinocytes or immune cells, which in most skin diseases are mainly located within the dermis. Hyperkeratotic skin lesions with thick epidermal layers and scaling make compound penetration more difficult. Cells and cytokines in immune-mediated skin diseases are well studied,[182–184] leading to many clinical trials focusing on the efficacy and safety of JAKinibs in dermatology.[185] While topical glucocorticoids belong to the most potent anti-inflammatory compound class, their long-term use ultimately leads to telangiectasia, striae, easy bruising, hypertrichosis and most importantly skin atrophy with subsequent wound healing deficits. Moreover, in some types of chronic skin inflammation like psoriasis, a rebound phenomenon typically appears after

Table 3 Clinical developmental stages of topical JAKinibs for skin diseases

Disease	JAKi	Target	Route	Phase of development	Trial identifier
Alopecia areata	Ruxolitinib	JAK1/JAK2	Topical	Phase II	NCT02553330
	Tofacitinib	JAK1/JAK3	Topical	Phase II	NCT02812342
	Ifidancitinib	JAK1/JAK3	Topical	Phase II	NCT03759340
Atopic dermatitis	Ruxolitinib	JAK1/JAK2	Topical	Phase III	NCT03745651
			Topical	Phase III	NCT03745638
			Topical	Phase I (paediatric)	NCT03257644
			Topical	Phase I	NCT03920852
	Delgocitinib	Pan-JAK	Topical	Phase II	NCT03725722
			Topical	Phase I	NCT03826901
	Tofacitinib	JAK1/JAK3	Topical	Phase II	NCT02001181
	Brepocitinib	JAK1/TYK2	Topical	Phase II	NCT03903822
	Ifidancitinib	JAK1/JAK3	Topical	Phase II	NCT03585296
Chronic hand eczema	Delgocitinib	Pan-JAK	Topical	Phase III	NCT04871711
			Topical	Phase III	NCT05355818
			Topical	Phase II	NCT02664805
Cutaneous GVHD	Ruxolitinib	JAK1/JAK2	Topical	Phase II	NCT03395340
			Topical	Phase II	NCT03954236
Discoid lupus erythematosus	Delgocitinib	Pan-JAK	Topical	Phase II	NCT03958955
Healthy	PF-06263726	Pan-JAK	Topical	Phase I	NCT01981681
Hidradenitis suppurativa	Ruxolitinib	JAK1/JAK2	Topical	Phase II	NCT04414514
Lichen planus	Ruxolitinib	JAK1/JAK2	Topical	Phase II	NCT03697460
Necrobiosis lipoidica	Ruxolitinib	JAK1/JAK2	Topical	Phase II	NCT04492618
Psoriasis	Ruxolitinib	JAK1/JAK2	Topical	Phase II	NCT00820950
			Topical	Phase II	NCT00617994
			Topical	Phase II	NCT00778700
	Tofacitinib	JAK1/JAK3	Topical	Phase II	NCT01831466
			Topical	Phase II	NCT01246583
			Topical	Phase II	NCT00678561
			Topical	Phase I	NCT02193815
	PF-06700841	JAK1/TYK2	Topical	Phase II	NCT03850483
Vitiligo	Ruxolitinib	JAK1/JAK2	Topical	Phase III	NCT04057573
			Topical	Phase III	NCT04052425
			Topical	Phase III	NCT04530344
			Topical	Phase II	NCT02809976
			Topical	Phase II	NCT03099304

GVHD, graft-versus-host disease; JAK, Janus kinase; JAKinibs, JAK-inhibitors.

termination of topical glucocorticoids. Thus, alternative immunosuppressive agents like the class of JAKinibs that do not result in skin atrophy or telangiectasia may be advantageous and could, given equal or better efficacy and a more tolerable safety profile, widely replace topical glucocorticoids.

Topical JAKinibs have been tested in the setting of a variety of inflammatory skin conditions including AA, AD, chronic hand eczema, cutaneous GVHD, discoid lupus erythematosus, hidradenitis suppurativa, necrobiosis lipoidica, psoriasis and vitiligo, as summarised in table 3. Most of the JAKinibs tested in skin diseases are applied as creams. Exceptions include tofacitinib, which is applied in an ointment and ATI-502, which has been developed as a solution.

The number on clinical trials or case series on the use of topical JAKinibs has increased over the last few years. One case series reports on the use of either tofacitinib ointment or ruxolitinib cream in paediatric patients with AA. Regrowth of hair was reported in four out of six patients.[186] Both JAKinibs, tofacitinib and ruxolitinib as topical formulations are now studied in phase II trials for AA. A further JAKinib, ATI-502 as solution is also in phase II for AA. In two phase III trials oral baricitinib was superior to placebo with respect to hair regrowth in patients with severe AA.[121] Topical tofacitinib has also been tested for AD. Results from a phase II trial showed significant improvement of AD clinical scores like the eczema area and severity index (EASI), physician global assessment and body surface area. Importantly, pruritus also improved when the JAK1/JAK3 inhibitor was applied to the skin. Of note, the median plasma tofacitinib concentrations detected were very low (0.31–0.70 ng/mL).[187] Likewise, ruxolitinib showed clinical improvement in AD in a phase II study.[188] Topical ruxolitinib was well tolerated and no safety concerns or clinically significant application-site reactions appeared when compared with vehicle control.[188] Subsequently, ruxolitinib has completed two phase III studies (TRuE-AD1 and 2) each with >500 patients. Treatment success was seen in 50% of subjects taking the 1.5% ruxolitinib cream compared with 8%–15% in vehicle controls after 8 weeks.[189] Consequently, ruxolitinib cream has been approved by the FDA for this condition.

A JAKinib with a novel three-dimensional spiro motif is delgocitinib.[190] This compound seems to show improved physicochemical properties for local application and showed efficacy

in skin inflammation in preclinical models.[191 192] Delgocitinib has gone through phase I–III studies for patients with AD demonstrating significant improvement in the EASI score[193 194] and has been approved in Japan for the treatment of AD. As recently published, the modified (m)EASI-50 was achieved by 51.0% of patients compared with 11.5% that received vehicle control and mEASI-75 was observed in 26.4% of treated patients compared with 5.8 with mEASI-75 response that received vehicle control treatment at week 4. The adverse events in patients that were treated with the topical JAKinib were reported to be mild and not related to the compound.[194] Long-term safety data demonstrated the absence of skin atrophy or telangiectasia, typical side effects of skin applied glucocorticosteroids.[195] In vitro studies showed blockade of JAK1-3 and TYK2 and therefore delgocitinib is considered as a pan-JAK inhibitor.[196]

Delgocitinib has been tested in patients with chronic hand eczema. A treatment period of 8 weeks achieved treatment success in 46% of patients receiving the pan-JAKinib in an ointment compared with 15% treated with the vehicle control during a phase II trial.[197] A 16-week phase IIb trial confirmed the efficacy of delgocitinib for chronic hand eczema.[198] First approval for the use of this topical pan-JAKinib for chronic hand eczema is expected. As reported for its use in AD, topical delgocitinib was generally well tolerated. A Japanese phase III trial demonstrated efficacy and safety of delgocitinib 0.5% ointment two times per day in patients with moderate-to-severe AD.[194] Delgocitinib ointments with 0.25% or 0.5% were tested in paediatric patients with AD. Topical delgocitinib (Corectim; 0.25% and 0.5%) is approved in Japan for the treatment of children and adults with AD. The other advanced-stage topical JAKinib developed for the treatment of AD is ruxolitinib. Data from two phase III trials demonstrated EASI-75 and EASI-90 responses in 61.8%–62.1% and 43.4%–44.3% of patients, respectively at week 8 (vehicle control at week 8 showed 14.4%–24.6% EASI-75 and 4.2%–9.5% EASI-90 responders). The FDA-approved ruxolitinib (Opzelura) for the topical treatment of patients aged 12 years and older with AD. Other skin diseases, where topical JAKinibs are under phase II clinical investigation include cutaneous GVHD, discoid lupus, hidradenitis suppurativa, lichen planus and necrobiosis lipoidica.

In psoriasis, topical JAK1/2 inhibition improved lesion thickness, erythema and scaling compared with placebo. When testing the plasma, nanomolar concentrations (0.32–2.10 nmol/L) were detected in patients who received ruxolitinib.[199] Topical ruxolitinib treatment of psoriatic plaques decreased factors related to IL-17 expressing T helper cell responses, dendritic cell activation and epidermal hyperplasia.[200] The use of tofacitinib ointments in psoriasis is well tolerated and has been reported to lead to an improvement by 4–8 weeks of treatment with good tolerability.[201 202]

Several studies exist on the use of topical JAKinibs for the treatment of vitiligo, a skin disease characterised by a cytotoxic $CD8^+$ T cell response towards melanocytes.[183] Data from a phase II trial have been reported very recently. By measuring a 25% or higher improvement from baseline in facial vitiligo area scoring index (F-VASI), a significant number of patients treated with ruxolitinib cream reached improvement at week 24 compared with vehicle control cream.[203] Phase III trials on ruxolitinib cream for vitiligo (TRuE-V1 and TRuE-V2) in patients 12 years of age and older confirmed the positive effects of JAK inhibition on skin repigmentation. F-VASI-75 responses at week 24 were 29.8% and 30.9% using 1.5% ruxolitinib cream two times per day compared with the vehicle control cream two times per day with 7.4% and 11.4% of patients achieving F-VASI-75.[204] Common adverse events reported included application-site acne, nasopharyngitis and pruritus. While ruxolitinib cream (Opzelura) is already approved for the treatment of vitiligo by the FDA, EMA approval is pending.

Taken together, JAKinibs have the potential to become the modern anti-inflammatory topicals. They seem to be as effective as glucocorticoids and may replace them in the long-term run in terms of tolerability. Yet, topical JAKinibs need improvements in structure and penetration to show their efficacy in the skin. In some skin diseases, hyerproliferation and/or hyperkeratosis may limit their penetration as a deep penetration to, for example, hair follicular structures may be needed. Conversely, the success of JAKinibs as skin creams may be in part due to their enhanced absorption, which raises concerns about systemic absorption and related side effects. This has led to a new generation of topical JAKinibs that have enhanced tissue retention and minimal systemic absorption. LAS194046 and AZD0449, both inhaled JAKinibs, were shown to decrease allergic lung inflammation in rats.[205 206] The JAK1 inhibitor AZD0449 has completed (NCT03766399) and is recruiting (NCT04769869) for phase I trials in humans. Within a double-blind, randomised, placebo-controlled, phase I proof-of-activity study in adults with mild asthma, the JAK1 inhibitor GDC-0214, used as an inhaled formulation, caused dose-dependent reductions in exhaled nitric oxide.[207]

JAKINIBS AND COVID-19

The SARS-CoV-2 was initially described as the cause of severe acute viral pneumonia in Wuhan, China, in December 2019 leading to a global pandemic. Infection by SARS-CoV2 results in a protean disease named COVID-19 that often results in a severe acute respiratory distress syndrome which frequently requires mechanical ventilation. Despite an association with lymphopenia, patients with severe COVID-19 often present signs of an immune hyper-responsiveness which involves the activation of different immune cells, such as T helper cells, macrophages, dendritic cells and neutrophils. This hyperactivation results in abnormally high levels of pro-inflammatory cytokines and chemokines known as cytokine release syndrome (CRS; also called cytokine storm) and has been known to underlie the pathology of viral infections, which had already been observed in the pathogenesis of SARS and the Middle East respiratory syndrome. These patients present with abnormally elevated plasma levels of cytokines such as IL-1β, IL-1RA, IL-2, IL-6, IL-7, IL-10, GM-CSF, IFNγ, TNFα as well as chemokines such as IL-8, IP-10, monocyte chemoattractant protein 1, macrophage inflammatory protein (MIP)1α and MIP1β.

Besides antiviral drugs, the search for drugs to be used in patients with COVID-19 immediately focused on modulators of the hypercytokinaemia as an attractive approach to reduce COVID-19 mortality rate. In particular, IL-6 appears to be a major driver of acute inflammation and elevated levels of IL-6 in patient plasma have been correlated to respiratory failure in patients with COVID-19[208] and associated with increased risk of acute respiratory distress syndrome, myocardial damage and mortality. Elevated IL-6 is also seen in patients with cancer receiving either chimeric antibody receptor T cell therapy or immune check point inhibitors. Monoclonal antibodies against IL-6, such as tocilizumab and sarilumab, which are already used in those clinical settings, have been used in patients with COVID-19 to dampen the hyperinnate immune response observed in patients with severe COVID-19 with some degree of success.[209–212] Beside monoclonal antibodies specifically

targeting IL-6, approved drugs inhibiting IL-6/JAK/STAT signalling may represent a valuable tool. In particular, JAKinibs, such as baricitinib, tofacitinib, ruxolitinib and fedratinib have been reported to attenuate the host inflammatory response associated with massive pro-inflammatory cytokine and chemokine release.

Cell entry, the first step of SARS-CoV-2 infection, is mediated by the ACE2 receptor on host cells in lung epithelial cells as well as in other tissues including the oral mucosa, the gastrointestinal tract, kidney, heart and blood vessels. ACE2 receptor signalling is mediated by two members of the numb-associated kinase family, the adaptor protein 2-associated kinase 1 (AAK1) and the cyclin G-associated kinase. Among the many clinically approved kinase inhibitors, baricitinib has been predicted to have the highest affinity towards these two kinases. Of note, binding of some JAKinibs including ruxolitinib, baricitinib and fedratinib to AAK1 and BMP2K (Bike) had been previously shown and could be explained by conserved binding modes between numb-associated kinases and JAKs. In vitro experiments with tofacitinib suggested that this JAKinib did not possess the same inhibitory effects towards these other kinases.

Inhibition of the JAK-mediated signalling results in an impairment of IFN-driven responses including the antiviral response. Therefore, there are concerns on the use of these drugs which have been shown to effectively inhibit the expression of IFN-regulated genes for the management of COVID-19.

Infection of rhesus macaques with SARS-CoV2 showed that baricitinib treatment was associated with reduced pneumonia, inflammatory cytokine transcripts and reduction in lymphoid and myeloid cell infiltration. There was a reduction in neutrophil extracellular traps release as well as microvascular thrombosis.[213] The first sizeable clinical open-label study has reported in 113 patients who received a 2-week treatment with oral baricitinib (4 mg/day) combined with antivirals (lopinavir/ritonavir) compared with 78 patients who received the standard of care (SOC) therapy (hydroxychloroquine and lopinavir/ritonavir). Notably, the 2-week case fatality rate was significantly lower in the baricitinib-arm compared with SOC-treated patients (0% (0/113) vs 6.4% (5/78)). Moreover, intensive care unit admission was also significantly reduced (0.88% (1/113) vs 17.9% (14/78)) in patients receiving baricitinib compared with SOC patients. With the exception of anosmia, all clinical, laboratory, including CRP levels, and respiratory functions significantly improved after 1 week and SpO2 significantly improved at week 2. Moreover, only few adverse effects (transaminases increase in four patients, urinary infection in one patient and oral candidiasis in one patient) were observed.[214]

In a randomised controlled trial, the Adaptive COVID-19 Treatment Trial (ACTT)-2,[215] the combination of remdesivir plus baricitinib (515 patients) was compared with remdesivir alone (518 patients) in moderate-to-severe COVID-19. The primary outcome was time to recovery. Patients who received both baricitinib and remdesivir recovered after a median of 7 days compared with 8 days in controls. And greater benefit was observed in patients who received supplemental oxygen or non-invasive ventilation at baseline. Interestingly, the beneficial effect was less pronounced in patients who did not require oxygen or who were intubated. A larger ACTT-4 (NCT04640168) was also performed and completed in 2021. Baricitinib in combination with remdesivir was compared with dexamethasone and remdesivir. This study showed that the two interventions were comparable effective.[216] Notably, no excess of thromboembolic events emerged from the ACCT-2 study with a similar incidence of thromboembolic events in both treatment arms. Given the findings reported by the ACCT-2 study, the FDA authorised an emergency use application for baricitinib usage in combination with remdesivir for patients with severe COVID-19, requiring supplemental oxygen, invasive mechanical ventilation or extracorporeal membrane oxygenation. Treatment with baricitinib in addition to SOC was associated with reduced mortality in hospitalised adults with COVID-19.[217 218] Furthermore, the double-blind, placebo-controlled study, COV-BARRIER, showed the efficacy of adding baricitinib to the SOC to treat patients hospitalised with COVID-19 (NCT04421027). Adding baricitinib (4 mg dose) to the SOC did not achieve statistical significance in the primary end point—patient progression to high flow oxygen, invasive mechanical ventilation, including ECMO, or death. Nonetheless, a significant reduction (38%) in death from any cause in all groups receiving baricitinib was observed.[219] Based on the above-metioned studies, the FDA approved baricitinib, as a monotherapy, for the treatment of patients with COVID-19 including children aged over 2 years requiring supplemental oxygen and non-invasive or invasive mechanical ventilation.

Tofacitinib has also shown superiority to placebo as a treatment for hospitalised patients with COVID-19 pneumonia (NCT04469114). Patients from 15 sites were randomised to tofacitinib or placebo along with local SOC, including use of glucocorticoids, antibiotics, anticoagulants and antiviral agents. Tofacitinib treatment significantly reduced the risk of death or respiratory failure over a 28-day period.[220]

In a mouse model of CRS, ruxolitinib attenuated T cell activation, cytokine production and several pathological features associated with the hypercytokinemia. IFNγ deficiency significantly protected mice from lethal CRS by attenuating small bowel pathology, whereas IL-17A deficiency significantly increased mortality by augmenting small bowel pathology.[221] Efficacy and safety of ruxolitinib was reported in a phase II clinical trial,[222] although the primary end point was not met.

Overall, we still have an incomplete knowledge of the effects of SARS-CoV-2 infection, the role that cytokines and IFNs have in the context of the pathology and the balance between positive and negative aspects of the JAK-mediated signalling cascades. Limited and controversial data have been reported on the role of JAKinibs on incidence and severity of COVID-19 infection in patients under JAKinib treatment.[223 224]

Why are JAKinibs so efficacious?

Due to their central role in cytokine receptor signalling (figure 1), participating in a broad array like IL-6, IL-2, IL-12/23 and IFNs it is clear that JAKinibs impact multiple pivotal functions, including antiviral properties. Thus, in contrast to the focused activity of TNF inhibitors on a single inflammatory key factor, JAKinibs exert their efficacy not by their capacity to inhibit different cytokines at the same time, but rather by their potential to interfere with the signalling of cytokines that are differentially involved in the pathogenesis of particular diseases. Indeed, when we look at figure 1 and figure 3 in tandem, we can assume that JAKinibs have efficacy in RA due to their interference with IL-6 signalling, in PsO, PsA and IBD due to their inhibition of the IL-23 pathway and thus generation of Th17 cells. Their side-effect profile (eg, anaemia, HZ), though, may be due to the simultaneous inhibition of signalling by IFNs and growth factors. Indeed, similar to the above-mentioned combination of bDMARDs targeting different pathways, the efficacy of JAKinibs does not appear to exceed that of the most efficacious bDMARDs, but their safety profile is different and includes adverse events not commonly seen on treatment with individual bDMARDs. Indeed, at higher doses of JAKinibs, which were tested in phase III trials, such as

JAK			Infections		Hematologic		Liver and GIT	Thrombosis	Lipids	Others	Malignancies
			Serious	URT	NEU	LYM	TA	VTE	HDL	CREA	Malignancies
			OI	HZ	Hb	PLT	GIP	PE	LDL	CPK	NMSC
Non-selective	Tofacitinib	JAK1-3	↑	↑	↓	↑	↑	↑*	↑	↑	↑*
			↑	↑↑	↔	↑	↔ (?)	↑*	↑	↑	↔ (?)
	Peficitinib	JAK1-3	↑	↑	↓	↓	↑	↔ (?)	↑	↑	↔ (?)
			↑	↑↑	↓	↔	↔ (?)	↔ (?)	↑	↑	↔ (?)
	Baricitinib	JAK1,2	↑	↑	↓	↔	↑	↑	↑	↑	↔ (?)
			↑	↑↑	↓	↑	↔ (?)	↑ (?)	↑	↑	↔ (?)
Selective	Upadacitinib	JAK1,2	↑	↑	↓	↓	↑	↔ (?)	↑	↑	↔ (?)
			↑	↑↑	↓	↓	↔ (?)	↔ (?)	↑	↑	↔ (?)
	Filgotinib	JAK1	↑	↑	↔	↔	↔	↔ (?)	↑	↔	↔ (?)
			↑	↔	↑	↓	↔ (?)	↔ (?)	↑	↑	↔ (?)

Figure 5 Side effects of selective versus non-selective JAKinibs. *In patients with cardiovascular or VTE risk factors at baseline. Arrows indicate the respective adverse event risk compared with placebo treatment with an slightly (↑), highly (↑↑), lower (↓) or similar (↔) risk. Question marks in brackets highlight areas of uncertainty, especially for safety events that need exploration in large observational studies. JAK, Janus kinase; HZ, herpes zoster; CREA, creatinine; URT, upper respiratory tract; NEU, neutrophils; LYM, lymphocytes; Hb, haemoglobin; PLT, platelets; TA, transaminases; GIT, gastrointestinal tract; GIP, gastrointestinal perforations; VTE, venous thromboembolism; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CPK, creatine phosphokinase; NMSC, non-melanoma skin cancer; OI, opportunistic infection.

10 mg two times per day of tofacitinib or 30 mg once daily of upadacitinib, the benefit-risk profile was not acceptable, just as seen for DMARD combinations.

Safety of approved JAKinibs

Since the JAK-STAT pathway is used by a wide array of hormones, growth factors, colony-stimulating factors and cytokines, its function is pleiotropic. Consequently, blockade of the JAK-STAT pathway leads to a number of predictable side effects. Although evidence from clinical trials in RA,[225] psoriasis[226] and IBD[91] support an acceptable benefit-risk profile, one must also consider off-target binding at higher doses, as well as idiosyncratic drug hypersensitivity, drug allergies and drug-drug interactions.[227] Safety concerns include effects on haematopoiesis, innate and adaptive host defence as well as cell growth; overall though, large studies have demonstrated an acceptable safety profile for many (but not all) patient populations investigated[228–230] (figure 5).

Tofacitinib, the first JAKinib licensed for indications outside of cancer treatment, was approved for RA in 2012 by the FDA but not until 2017 by EMA. The approval by the FDA was contingent on a phase IIIb/IV study to monitor all adverse effects associated with tofacitinib therapy. This was named the ORAL-SURVEILLANCE study, which has recently published its findings. The trial included 4362 patients with moderate-to-severe RA despite previous MTX treatment, who were above 50 years of age and had at least one additional cardiovascular (CV) risk factor. The participants were randomly assigned to receive tofacitinib 5 mg or 10 mg two times per day or a TNF inhibitor (either adalimumab or etanercept) and were followed for up to 6 years. The trial's co-primary end points of non-inferiority of tofacitinib versus TNF inhibitor in major adverse cardiovascular events (MACEs) and cancer was not met. A higher risk of developing MACE was reported with an HR with any dose of tofacitinib versus TNF inhibitors of 1.33 (95% CI 0.91 to 1.94) resulting in a number needed to harm (NNH) of 412 (567 for TOFA5 two times per day and 319 for TOFA10 two times per day) and for developing cancer (excluding non-melanoma skin cancer (NMSC)), with an HR of 1.48 (95% CI 1.04 to 2.09) and an NNH of 275 (276 and 275 for for TOFA5 two times per day

and TOFA10 two times per day, respectively) both crossing the predefined upper 95% CI of 1.8.[231]

Based on the ORAL-SURVEILLANCE study, the FDA determined in late 2021 that there is an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots and death for patient treated with tofacitinib, assumed most JAKinibs as functionally equivalent and requested new and updated safety data for baricitinib and upadacitinib. The FDA also determined that JAKinibs should only be used after one or more TNF inhibitors have failed or are contraindicated.

In early 2022, the task force developing an update of the EULAR recommendations for the management of RA also evaluated the data of the ORAL-SURVEILLANCE trial which warranted a change compared with the 2019 version.[232–234] First, the EULAR Task Force took into account that data for other JAKinibs than tofacitinib do not exist beyond registers or rather long-term extensions of trials and, therefore, one cannot exclude that a similar risk might also be observed with other JAKinibs. On the other hand, only patients with defined risk factors have been studied in ORAL-SURVEILLANCE, while registry data and LTEs of trials did not show any differences between anti-TNFs and JAKinibs in general RA populations. Based on these assessments, JAKinibs were separated from bDMARDs in the respective element and it was recommended that in patients with RA with IR to csDMARDs, JAKinibs may be used only after assessment of defined risk factors for MACEs, venous thromboembolism (VTE) and malignancy; these risk factors are then listed (see also below).

In October 2022, based on a review conducted by the Pharmacovigilance Risk Assessment Committee, EMA has concluded that the identified risks apply to all JAKinibs approved for the treatment of chronic inflammatory disorders such as RA, PsA, JIA, axial spondyloarthritis, UC, AD and AA. EMA recently recommended that in patients aged 65 years or above, those at increased risk of major CV diseases (heart attack or stroke), those who smoke and those at increased risk of cancer, JAKinibs should be used with caution and only if no suitable alternatives exist. JAKinibs should also be used with caution in patients with risk factors for VTE. Furthermore, doses should be reduced in patient groups who are at risk of VTE, cancer or major CV problems, where possible.

The profile of newer JAKinibs appear comparable with possible differences in infection rates, and haemoglobin changes. Rates in herpes zoster (HZ) infections appeared different (and without any increase compared with placebo or TNF inhibitor treatment) in randomised controlled trials investigating filgotinib, while other JAKinibs do show increased HZ rates. However, the interpretability of safety signals derived from clinical drug development programmes is limited for several reasons: (1) most trials include a selective patient population (not representative of the general population or the patient population in clinical routine), (2) even large randomised controlled trials provide relatively small patient numbers and (3) relatively short observation periods. In the light of usage of these compounds in potentially multimorbid patients with chronic IMIDs that may demand life-long therapy, the identification of rare safety signals is increasingly challenging.[231] In an integrated safety analysis of the long-term extension studies in patients with RA, PsA, AD and AS treated with upadacitinib, comprising >6000 patients and 15 000 patient-years of exposure, the rates of malignancies (excluding NMSC), MACE and VTE was similar between upadacitinib and the active comparators adalimumab and MTX, respectively. Increased rates of HZ were observed in the RA and PsA population, whereas NMSC, serious infections and opportunistic infections were observed to be more frequent in upadacitinib (compared with adalimumab)-treated patients in PsA.[235] Additional long-term safety studies are necessary to find definite conclusions regarding safety profiles of pan versus selective JAKinibs. This cannot be emphasised enough when discussing the safety of JAKinibs with our current experience.

Infections rates

The most common infections in clinical trials from patients with RA included nasopharyngitis, upper respiratory infections, gastroenteritis or bronchitis. Increased infection rates were observed in a systematic review investigating safety events, especially HZ, tuberculosis, cellulitis, panniculitis, septic shock and osteomyelitis.[236] A higher risk for opportunistic infection, primarily owing to HZ infections were observed for patients treated with tofacitinib as compared with TNF inhibitors.[231] Accordingly, most recent EULAR recommendations consider the use of HZ vaccinations for patients with rheumatic diseases.[237 238] Recent reports showed that the risk of serious and fatal infections was further increased in elderly patients above 65 years of age.[239] Therefore, the EMA recommended that tofacitinib should only be considered in these patients if no suitable alternative treatment is available.

The risk for developing HZ may be further influenced by concomitant use of glucocorticoids or MTX and also higher rates in certain populations, as clinical JAKinibs studies in Asian patients suggest.[225 240–244] The exact mechanism remains unclear but in part may be explained by the importance of JAK-dependent cytokines in driving the development and functions of NK cells, which are important for controlling viral infections, although NK cell counts are not markedly reduced in patients treated with JAKinibs. Reduced IFNγ activity and subsequent reduced activity of neutrophils may explain an increased rate of oral candidiasis.

Nephropathy

A larger multicentre clinical trial also showed a higher incidence (14%–18%) of BK virus-associated nephropathy in renal transplant recipients treated with tofacitinib compared with ciclosporin (6%)[245 246] also in combination with mycophenolate mofetil and at relatively high doses. High dose of baricitinib was also associated with BK nephropathy and BK viraemia in patients with genetic autoinflammatory disease.[247] Elevations of creatinine have been observed under JAKinib treatment but have not been associated with renal failure or other clinical sequelae.[248 249]

Gastrointestinal perforation

Possible increased risk of gastrointestinal perforations was recognised in patients with RA treated with tofacitinib (all treated with glucocorticoids or NSAIDs).[225] In August 2020, regulators in the UK have issued a warning regarding an increased risk of diverticulitis based on increased rates of diverticulitis with several patients experiencing intestinal perforations in clinical trials and postmarketing studies. Numerically higher rates of gastrointestinal perforations were observed in three upadacitinib studies compared with placebo.[129 132 133]

Risk of thrombotic adverse events

Epidemiological studies have shown that patients with RA are in general at risk of VTE compared with control populations.[250 251] Therefore, concerns have been raised as to whether the usage of JAKinibs in RA further increases that risk. In

ORAL-SURVEILLANCE patients treated with 10 mg tofacitinib two times per day showed an increased risk for developing VTE and pulmonary embolism (PE), whereas no increased risk was observed for 5 mg tofacitinib two times per day.[231] History of VTE, use of oral contraceptives, GC use, increased body mass index, antidepressant use, male gender and age above 65 years were associated factors with VTE/PE, while usage of protone pump inhibitors appeared protective. A large cohort study in >50 000 patients comparing tofacitinib versus TNF inhibitors found a numerically higher, but statistically non-significant, risk of development of VTE.[252]

A post hoc analysis of safety data from large populations of patients with RA, PsO and PsA treated with tofacitinib assessed the risk of VTE and arterial thromboembolism (ATE), including analyses stratified by the baseline CV or VTE risk factors. Integrated safety analysis across the whole tofacitinib development programme suggested an increased risk for VTE, PE and ATE in patients with pre-existing CV and VTE risk factors.[253]

Curiously, the association of VTE/PE risk in patients with myeloproliferative disease receiving ruxolitinib suggests a protective effect of JAK inhibition. Myeloproliferative disease carries a significant risk of VTE/PE that is thought to be related to increased blood viscosity associated with a raised haematocrit.[254] There is a mixed evidence that the presence of JAK2 mutations increases this risk[254] and conversely equally mixed evidence that risk of VTE is decreased by ruxolitinib.[255] This may be a reflection on its use in a different indication/patient group or due to the drug itself.

A recent multidatabase analysis comparing baricitinib with TNF inhibitors identified an increased risk for VTE (incidence rate ratio: 1.51; 95% CI 1.10 to 2.08) in baricitinib-treated patients,[256]one of the reasons for FDA to approve only the lower dose of baricitinib (2 mg/day) for the treatment of RA, while in most other regulatory areas the 4 mg dose is also approved. However, the results of this study were mainly driven by one of the registries and not observed by others. A randomised prospective study is currently being conducted to adequately address this question.

As yet, no clear signal for VTE/PE in upadacitinib and filgotinib trials was observed. However, package labels include warnings especially for patients with risk factors for VTE. While the JAKinibs mechanism of action leading to thromboembolism remains unclear, similar signals have been identified in multiple members of the family. If JAK selectivity plays a role remains an open debate and specifically designed safety studies comparing selective and unselective JAKinibs in a head-to-head setting are needed to evaluate risk differences of VTEs.

Haematological adverse events

Given that many haematopoietic growth factors including EPO, TPO and G-CSF signal through JAK2, changes in laboratory parameters are not unexpected. Anaemia was reported in patients treated with ruxolitinib, baricitinib, upadacitinib and peficitinib.[257] While small changes in haemoglobin levels were observed in a pooled analysis of tofacitinib patients on a group level, only few patients experienced clinically meaningful haemoglobin changes.[258]

An inverse correlation was observed for the increase in haemoglobin and disease activity, suggesting that reduction of inflammation counterbalances the minor negative effects of tofacitinib in erythropoiesis.[258] A possible reason for a smaller increase in haemoglobin with tofacitinib 10 mg two times per day is a dose-associated inhibition of JAK2, which is not observed at the lowest 5 mg two times per day dose. The greater decrease in haemoglobin levels in ruxolitinib-treated and baricitinib-treated patients as compared with tofacitinib-treated patients might in part be explained by their potent inhibition of JAK2. Reductions in haemoglobin levels seem to be dose dependent and only rarely clinically significant.[259] Of note, however, it is a question of inducing anaemia and a question of reversing anaemia of chronic disease, which allows to draw conclusions on JAK2 inhibition. Anaemia is not reversed with tofacitnib, bacricitinib, peficitinib or upadacitnib, suggesting in vivo JAK2 inhibition by all these drugs. Only filogitinib improved haemoglobin levels in clinical phase II and phase III trials, and no increased incidence of anaemia was observed in patients treated with filgotinib.[144 146]

JAK1 and JAK3 play an essential role in lymphocyte survival and maturation and therefore all JAKinibs have been associated with lowered lymphocyte counts. Monitoring of lymphocyte counts is recommended since lymphopenia was associated with a slightly higher overall infection rate and therefore JAKinib should be interrupted when lymphocyte count is $<1.0\times10^9$ cells/L. Thrombocytosis reflects disease activity in patients with RA and suppression of inflammation should reduce platelet number. While treatment with tofacitinib is associated with a decrease in platelets, an early increase in thrombocytes on baricitinib was observed, but did not appear to be associated with an increased risk for VTEs. In contrast to rheumatological patients, the use of JAKinibs in haematological patients is associated with a higher incidence of cytopenias. However, as all FDA-approved JAKinibs are competitive antagonists their effect can be overcome by pharmacological doses of cytokines. Thus, it is possible to use EPO, TPO and G-CSF to reverse the cytopenias associated with JAKinib use but maintain their effectiveness as immunosupressants in this patient group.

Malignancies

One particular concern with long-term suppression of the JAK/STAT pathway is the possible development of malignancies. Both type I and II IFNs play an important role in the process of immunoediting, which is critical for the antitumour immune response. In post-transplant patients treated with tofacitinib, the risk of lymphoproliferative malignancy was increased by JAK inhibition. However, it has to be considered that the doses of tofacitinib used in these trials were higher than the approved dose for RA and that the patients were also treated with concomitant immunosuppressants. Phase II and phase III trials for autoimmune diseases did not show an increased cancer risk associated with tofacitinib treatment.[260] The risk to develop lymphoma or other malignancies based on data from the RA clinical trial data and pooled analysis of UC studies was low.[243 261] However, data from ORAL-SURVEILLANCE (see above) showed an increased risk of malignancies (excluding NMSC) in tofacitinib-treated patients, receiving either the approved dose of tofacitinib 5 mg two times per day or 10 mg two times per day in comparison to TNF inhibitors (etanercept or adalimumab)-treated patients. All patients included in the study were on stable background DMARDs when entering the trial. Patients receiving tofacitinib 10 mg two times per day were switched to 5 mg two times per day as a result of a protocol modification in 2019 due to safety concerns of the 10 mg two times per day dosing. Non-inferiority was not demonstrated, as the upper limit of the HR's 95% CI crossed the predefined margin of 1.8. HR for cancer (excluding NMSC) were 1.48 (1.04 to 2.09) in the combined tofacitinib group. HRs for tofacitinib 5 mg two times per day and 10 mg two times per day arms (vs TNF inhibitor) were 1.47 (1.00 to

2.18) and 1.48 (1.00 to 2.19), respectively. The most common malignancies observed were lung cancer and lymphoma. Also, non-adjudicated rates of melanoma skin cancer were higher in the tofacitinib arms.[231] Consequently, a warning regarding the use of JAKinibs in patients with a risk of malignancy, especially smokers and previous smokers, has been raised.

Lipid profile and cardiovascular adverse events

Elevation of serum lipids have been seen in patients with RA receiving IL-6 receptor blocker tocilizumab.[262] IL-6 is known to lead to insulin resistance and to support the redistribution of fatty acids from the blood to peripheral tissues which can cause low serum levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides. Accordingly, increase in LDL, HDL were observed in patients treated with approved JAKinibs and may be secondary to blocking of IL-6 signalling. However, long-term extension studies have not shown a higher incidence of CV events.[225] Moreover, the ENTRACTE trial, which had a study design similar to ORAL-SURVEILLANCE, did not show any difference between tocilizumab and anti-TNF regarding MACEs[263]; this implies that the data seen in ORAL-SURVEILLANCE are unlikely to have been mediated by the inhibition of IL-6 signalling by tofacitinib. Elevation of serum lipids have been observed by 12 weeks and are generally stable thereafter with an incidence of CV events similar to placebo. LDL and HDL ratio remained stable after 24 months.[225 264–268] Treatment with atorvastatin has been shown to be effective in patients with elevations in cholesterol on tofacitinib.[269] Only minor, not clinically meaningful elevations of lipid levels were observed in filgotinib-treated patients in a pooled safety analysis of phase III studies.[238] According to an international consensus, lipid levels should be assessed every 3 months in patients treated with JAKinibs and if increased, managed according to national guidelines.[270]

Regarding major adverse CV events, recent findings from the ORAL-SURVEILLANCE postmarketing trial suggested that tofacitinib was associated with higher rates of MACE than TNF inhibitors in patients with RA at high CV risk. Incidence rates of MACE, defined as CV death, non-fatal myocardial infarction or non-fatal stroke, were 0.91 for patients receiving tofacitinib 5 mg two times per day, 1.05 for those treated with tofacitinib 10 mg two times per day and 0.73 per 100 person-years for those treated with a TNF inhibitor. The estimated HR for occurrence of MACE with any dose of tofacitinib relative to the TNF-inhibitor group was 1.33 (95% CI 0.91 to 1.94).[231] In an exploratory post hoc analysis of ORAL-SURVEILLANCE, it was suggested that the increased MACE risk appears to be markedly higher in patients with RA with a history of atherosclerotic CV disease (ie, coronary artery disease, cerebrovascular disease or peripheral artery disease), compared with patients without a history of atherosclerotic CV disease.[271]

In a large multidatabase, population-based study including 102 263 patients with RA, tofacitinib was not associated with an overall risk of composite CV outcome compared with TNF inhibitors treated in the real-world setting. However, in patients with baseline CV risk factor or history of CV disease tofacitinib is associated with an elevated risk of CV events.[272] More data for baricitinib, upadacitinib or filgotinib are required to address similar safety aspects due to shared mechanisms of action with tofacitinib. A phase IV study, comparing the safety of baricitinib versus TNF inhibitors with respect to venous VTEs when given to participants with RA is currently ongoing (NCT03915964).

Potential teratogenicity and fertility

It is reasonable to assume that JAKinibs cross the placenta from the beginning of pregnancy. In animal studies, tofacitinib was teratogenic and feticidal when used at doses several times higher than those used in humans.[273] No fetal deaths or congenital malformations were observed in the clinical development programmes for RA, psoriasis or IBD.[274 275] However, the safety of JAKinibs during pregnancy or breast feeding has not been well established in larger cohorts and, therefore, their use in these patient populations should currently be avoided. No data are available on breast feeding with JAKinibs. However, small molecules are present in lactating rat milk, therefore breast feeding should be avoided. In preclinical animal studies, an effect of filgotinib treatment on spermatogenesis was observed, which was not seen with other JAKinibs. Studies investigating this effect (NCT03926195, NCT03201445) remain unpublished at the timepoint of writing this manuscript, however, a press release stated that no increased risk for impaired spermatogenesis was observed in two randomised controlled trials (MANTA and MANTA-RAY).[276]

Other laboratory variables

A randomised controlled trial assessed changes in serum creatinine and glomerular filtration rate in patients with RA. Tofacitinib-treated patients with RA showed a mild increase in creatinine levels and a decrease in glomerular filtration rate, which reversed on drug discontinuation.[228 249] Slight elevations in serum creatinine rates have been observed across all JAKinib studies but were not associated with nephropathic changes or a clinical correlate leading to end-stage renal disease. Slight elevations of transaminases have been observed for all the approved JAKinibs, except for filgotinib. Abnormalities resolved after reduction or discontinuation. However, monitoring of liver function tests after initiation and during JAKinib treatment is recommended. Creatine phosphokinase elevations have been noted with all JAKinibs but have generally been asymptomatic and did not lead to rhabdomyolysis.

CONCLUSION AND FUTURE PERSPECTIVES

Inhibition of type I/II cytokine signalling through the use of JAKinibs has been a great success in the treatment of a variety of autoimmune diseases and haematological malignancies and in the increasingly recognised cytokine release syndromes driven by the use of cancer immunotherapies, the appearance of COVID-19 and other macrophage activation syndromes.

However, the use of JAKinibs has been limited by adverse events, both when applied as a monotherapy and in combination with other immuno-modulatory agents. For certain adverse events, such as MACE, malignancy and VTE, patients at risk can be identified, and for others, such as HZ, prevention by vaccination should be implemented. Regarding combination of therapy, the best regimens are yet to be fully established for some of the diseases—for RA it is usually combination with MTX.

Despite an increasing amount of work in the recent years, the importance of selectivity for an effective treatment response and also regarding reduction of adverse events still remains unclear. The introduction of increased selectivity of JAKinibs has hitherto resulted only in a limited reduction of adverse effects. Highly specific inhibitors of JAK1 are still able to block many families of cytokines and highly specific inhibitors of other JAKs have been less successful therapeutically. Nevertheless, there may be some interesting differences in the safety profile of highly selective versus less selective agents, but this still needs to be ascertained.

Moreover, TYK2 inhibitors appear efficacious in certain diseases and may exhibit a different safety profile compared with JAK1, 2, 3-inhibiting agents, thus holding some promise in the future for certain disorders.

The use of topical JAKinibs either as creams in dermatology or inhalers in respiratory medicine offers an alternative strategy to overcome side effects of this group of drugs. Even when used systemically, JAKinibs exert their effects rapidly and are quickly cleared from the body. This may lead to their use as short-term agents during the early stages of transplantation or prior to the use of a more slowly acting biological therapy.

While we have made much progress and gained many insights regarding JAKs and their inhibition over the last decade, many unanswered questions remain in this rapidly progressing field and await further elucidation. These questions include, but are not limited to: which JAKs drive protection from HZ? Which JAKs are responsible for protection from clotting and MACEs? Which JAKs protect from malignancies? Which specific pathway are targeted by the same JAKinibs in different diseases? Answers to these questions will allow for a safer use of JAKinibs, and may provide clues for novel therapies against thrombosis and the development of malignancies.

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ORCID iDs
Michael Bonelli http://orcid.org/0000-0002-6122-7482
Andreas Kerschbaumer http://orcid.org/0000-0002-6685-8873
Kastriot Kastrati http://orcid.org/0000-0002-1393-3390
Leonhard X Heinz http://orcid.org/0000-0002-6921-1493
Daniel Aletaha http://orcid.org/0000-0003-2108-0030

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