JAK inhibition as a therapeutic strategy for immune and inflammatory diseases

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Abstract | The discovery of cytokines as key drivers of immune-mediated diseases has spurred efforts to target their associated signalling pathways. Janus kinases (JAKs) are essential signalling mediators downstream of many pro-inflammatory cytokines, and small-molecule inhibitors of JAKs (jakinibs) have gained traction as safe and efficacious options for the treatment of inflammation-driven pathologies such as rheumatoid arthritis, psoriasis and inflammatory bowel disease. Building on the clinical success of first-generation jakinibs, second-generation compounds that claim to be more selective are currently undergoing development and proceeding to clinical trials. However, important questions remain about the advantages and limitations of improved JAK selectivity, optimal routes and dosing regimens and how best to identify patients who will benefit from jakinibs. This Review discusses the biology of jakinibs from a translational perspective, focusing on recent insights from clinical trials, the development of novel agents and the use of jakinibs in a spectrum of immune and inflammatory diseases.

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The discovery of the numerous cytokines underlying the pathogenesis of allergic, inflammatory and autoimmune disorders has provided the basis for the development of highly successful therapeutic monoclonal antibodies (mAbs) and recombinant proteins that target several such cytokines and their receptors[1]. Such therapies have dramatically altered outcomes for a range of diseases, including rheumatoid arthritis, psoriasis and inflammatory bowel disease (IBD)[1]. However, even for a disease such as rheumatoid arthritis, in which much progress has been made, most patients do not completely respond to currently available therapies, and there are relatively few examples of long-term remission after cessation of therapy[2]. For other disorders — especially diseases in which fibrosis and tissue destruction are major features, such as systemic sclerosis — there has been even less progress.

Therefore, despite substantial advances, there is still a major need for novel therapeutic strategies for immune and inflammatory diseases. If targeting specific cytokines outside the cell is insufficient to reliably achieve complete remission, an obvious alternative strategy is to target the action of different cytokines inside the cell. However, given the complex molecular basis of cytokine action, this task can be a daunting one.

The Janus kinase (JAK) family is a small family of receptor-associated tyrosine kinases that are essential for the signal cascade downstream of type I and type II cytokine receptors. In this Review, we briefly discuss the role of JAKs in cytokine signalling, the rationale for targeting these kinases, the status of current jakinibs and future directions in this field including their potential utility in a wide variety of immune-mediated diseases. This discussion is especially timely now, as the first jakinibs are being approved and studied for broader indications, and newer, potentially more selective agents are being developed.

The rationale for targeting JAKs

The term 'cytokine' encompasses many structurally unrelated proteins that are grouped based on their binding to distinct receptor superfamilies, which include the tumour necrosis factor (TNF) receptor family, the interleukin (IL)-1 receptor superfamily, the IL-17 receptor superfamily, the transforming growth factor receptor superfamily, the receptor tyrosine kinase superfamily, the G protein-coupled receptor superfamily and the type I and type II cytokine receptor superfamily. Most relevant is that the different families use different modes of signal transduction.

Type I and type II cytokine receptors — which compose a family of receptors bound by over 50 cytokines, interleukins, interferons (IFNs), colony-stimulating factors (CSFs) and hormones — share a distinct intracellular signalling pathway mediated by JAKs (FIG. 1) — JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) — that bind directly to the intracellular domains of type I and type II cytokine receptors and not to other classes of cytokine receptor (FIG. 2).

JAK-dependent cytokines are major contributors to immunopathology. For instance, IL-6 is a prototypic pro-inflammatory cytokine commonly overexpressed in many autoimmune and inflammatory diseases[3] and a driver of acute phase responses including induction of C-reactive protein (CRP) and serum amyloid A[4]. The efficacy of monoclonal antibodies that target IL-6 or its receptor (IL-6R) in rheumatological diseases confirms the criticality of this cytokine in immunopathogenesis[3]. Similarly, the efficacy of ustekinumab — a monoclonal antibody targeting the p40 subunit of IL-12 and IL-23 — in treating IBD and psoriasis strongly supports the pathogenic roles of both cytokines in these diseases[5]. The overexpression of IL-4, IL-5 and IL-13 in allergic disease and the success of drugs that target these cytokines[6–8] provide yet another compelling argument for the potential utility of interfering with type I and type II cytokine signalling in disorders such as asthma and atopic dermatitis. Many other JAK-dependent cytokines have been shown in various settings to contribute to inflammatory diseases. Examples include but are not limited to IFNs, IL-15, IL-21, granulocyte CSF (G-CSF) and granulocyte–macrophage CSF (GM-CSF)[1].

The dependence of type I and type II cytokines on JAKs was established in a variety of genetic models from mutagenized cell lines and knockout mice to humans[1,9,10]. Polymorphisms in *JAK* and signal transducer and activator of transcription (*STAT*) genes are associated with autoimmunity, and loss-of-function mutations cause immunodeficiency due to the inability of type I and type II cytokines to transmit signals through their receptors[1,9,10]. Phosphoproteomic analysis has also established that at least 90% of IL-2 receptor signalling is JAK-dependent[11]. Therefore, the critical role of JAKs in type I and type II cytokine signalling strongly argues that interfering with the activity of these kinases could lead to a new class of immunomodulatory drugs[12,13] but also indicates some potential adverse effects of JAK blockade, for instance, cytopenia and infection.

Feasibility of targeting JAKs

As tyrosine kinases, JAKs transfer phosphates from ATP to tyrosine residues on other proteins, including cytokine receptors, JAKs themselves and downstream signalling molecules. Tyrosine phosphorylation of kinases, including JAKs, triggers their enzymatic activity. Additionally, tyrosine phosphorylation of receptors causes the recruitment of signalling molecules that bind to the phosphorylated tyrosines of the ligand-engaged receptor. One critical class of signalling molecule for type I and type II cytokine receptors is the STAT family of DNA-binding proteins (FIG. 1). Phosphorylated STATs translocate to the nucleus, bind to DNA and drive gene transcription. This simple pathway is essential for the effects of cytokines that bind type I and type II receptors, but is not used by TNF, IL-1, IL-17 or other cytokines[10].

In the early 2000s, the success of the tyrosine kinase inhibitor imatinib for the treatment of chronic myelogenous leukaemia provided startling evidence that targeting kinases was not only feasible but potentially game changing[14]. The oncology field moved ahead quickly, and, to date, 31 kinase inhibitors have been approved by the US Food and Drug Administration (FDA) for the treatment of various cancers[15,16]. Not surprisingly, the first jakinib to gain FDA approval was designed for neoplastic rather than immune-mediated diseases. A V617F mutation in *JAK2* is strongly associated with myeloproliferative neoplasms — including myelofibrosis, polycythaemia vera (PCV) and essential thrombocythaemia — and occurs in nearly 100% of patients with PCV and over 75% of patients with essential thrombocythaemia[17]. The JAK pseudokinase domain regulates kinase activity. Mutations in this domain of JAK2, including the V617F mutation, can result in constitutive activation downstream of erythropoietin (EPO), GM-CSF and thrombopoietin (TPO) receptors. V617F is an acquired mutation; therefore, proliferation is restricted to the lineage expressing the mutant allele. These observations provided strong rationale for the development of what became the first approved JAK inhibitor, ruxolitinib (FIG. 3), and its approval by the FDA in 2011 showed that JAK inhibition was not only possible but also safe and effective for these indications[18,19]. Indeed, the JAK–STAT pathway is constitutively activated in many cancers[9,20], which has led to the initiation of multiple trials testing jakinibs against haematological and solid tumours, including trials in which multiple kinase inhibitors are used in combination (for example, NCT02912754).

Although targeting kinases may be adequately safe in the context of neoplastic disorders, whether such drugs can be used in the long term in patients with immune-mediated disease is a very different question, particularly given the greater need for a 'clean' safety profile outside of life-threatening diseases such as cancer. A large body of evidence leading to the acceptance of jakinibs as a therapy for rheumatoid arthritis has started to answer this question and is now reviewed briefly.

Inflammatory arthritides

Rheumatoid arthritis. Tofacitinib (FIG. 3), a first-generation jakinib that inhibits JAK3, JAK1 and, to a lesser degree, JAK2, is the first jakinib developed for the treatment of autoimmune disease. Like other first-generation jakinibs, tofacitinib binds to and competitively inhibits the kinase domain of JAKs. It was studied in a variety of preclinical models from transplant rejection to arthritis[21–23]. More importantly, multiple clinical trials including six phase III trials studying tofacitinib in rheumatoid arthritis have been completed, encompassing more than 6,000 patients followed for as long as 8 years[24–28] (TABLE 1). These trials have shown that tofacitinib is efficacious for new and established disease[29], as monotherapy[30] or in combination with methotrexate

C-reactive protein
(CRP). A protein classified as an acute phase reactant and produced in the liver in response to inflammation.

Serum amyloid A
An acute phase reactant, produced predominantly in the liver and expressed at different levels in response to inflammatory stimuli.

Phosphoproteomic analysis
A proteome-wide analysis of phosphorylated proteins.

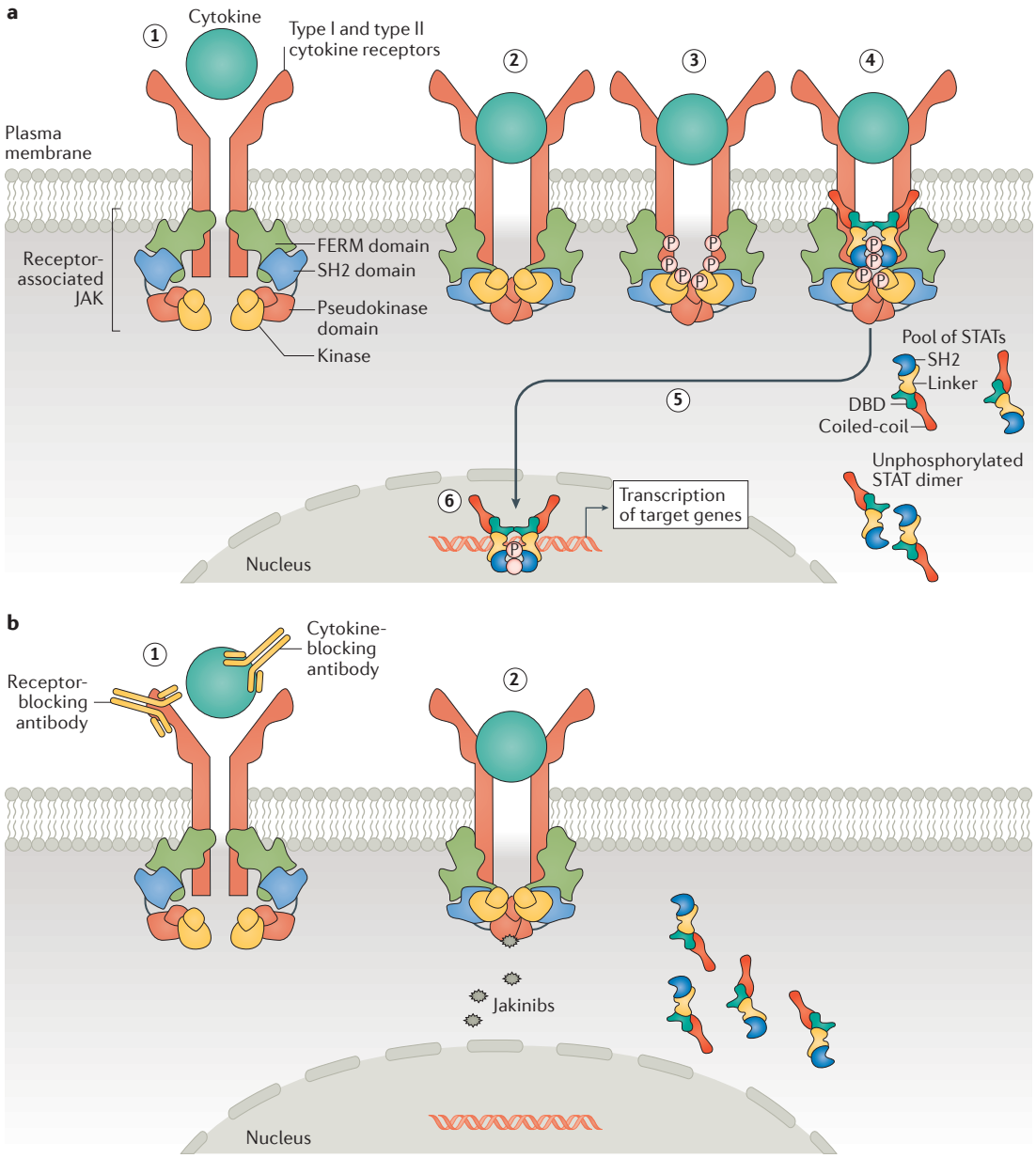

Figure 1 | **Signalling by type I and type II cytokine receptors. a** | Type I and type II cytokine receptors comprise subunits that physically associate with Janus kinases (JAKs). Type I and type II cytokine receptors do not have any enzymatic activity but instead depend on JAKs to transduce intracellular signals. JAK proteins share four components: the kinase domain, the pseudokinase domain, the four-point-one protein, ezrin, radixin, moesin (FERM) domain and the Src homology 2 (SH2)-like domain. The canonical JAK–signal transducer and activator of transcription (STAT) pathway is initiated by extracellular association of cytokines with their cognate receptors (step 1). In step 2, binding activates the receptor, resulting in apposition of receptor-associated JAKs. JAKs are tyrosine kinases; upon activation, they transfer phosphate from ATP to tyrosine residues on other proteins, including cytokine receptors and JAKs themselves. This event is important, as tyrosine phosphorylation of kinases, including JAKs, triggers their enzymatic activity (step 3). In steps 4–6, tyrosine phosphorylation of receptors creates docking sites for signalling molecules including STATs, which share an SH2 domain, a linker domain, a DNA-binding domain (DBD) and a coiled-coil domain. In canonical JAK–STAT signalling, STATs undergo JAK-mediated phosphorylation of their tyrosine residues, leading to STAT dimerization, nuclear translocation, DNA binding and target gene induction. Unphosphorylated STAT dimers also have regulatory functions, although these functions are less well defined. **b** | Monoclonal antibodies can block type I and type II cytokines and their receptors (step 1). By contrast, jakinibs block cytokine signalling by inhibiting kinase activity, thereby preventing JAKs from phosphorylating STATs and other substrates so that intracellular signals cannot be transduced (step 2). Because JAKs are critical for multiple different cytokines, jakinibs, unlike biologics, block the action of a range of cytokines. This range of activity could be useful in the substantial number of patients with autoimmunity who are refractory to or intolerant of treatment with biologics. First-generation jakinibs block multiple JAKs, whereas second-generation jakinibs may have more selectivity for JAKs and so may inhibit a narrow range of cytokines. Cytokine receptors, JAK and STATs are drawn based on structural information[203,204].

American College of Rheumatology 20%, 50% and 70% response criteria (ACR20, 50, 70). Standard criteria used to measure the effectiveness of treatments for rheumatoid arthritis. These criteria measure percentage improvement in tender or swollen joint counts and three of the following measures: patient assessment; physician assessment; pain scale; disability/functional questionnaire and acute phase reactants

(MTX)[28], and in both treatment-naive[27] and treatment-refractory patients[25,26]. Patients achieved significant amelioration of disease activity, as measured by the American College of Rheumatology 20%, 50% and 70% response criteria (ACR20, 50, 70)[24–26,31–33]. Patients also reported improvements in functional status measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) and 36-Item Short Form Survey (SF-36). Tofacitinib proved to be superior to MTX[24,27,34], non-inferior to the TNF inhibitor adalimumab[26] and effective in patients for whom multiple biologics such as TNF blockers, tocilizumab and abatacept had failed[35,36]. Moreover, tofacitinib was shown to prevent the progression of structural joint disease as assessed by conventional radiography and magnetic resonance imaging (MRI)[24,33,34]. The largest radiographic response was seen in patients with the most baseline structural damage, but improvement was also noted in other groups[37]. On the basis of these and other findings, tofacitinib, on a regimen of 5 mg twice daily (b.i.d.), was approved by the FDA in 2012 for the treatment of rheumatoid arthritis in patients who are intolerant or unresponsive to MTX[38]. Since then, its effectiveness has been confirmed in long-term extension studies that have tracked disease activity in >4,000 patients[2,39,31,40,41], especially studies in which disease activity measures incorporated CRP[42], which may reflect blockade of IL-6 signalling[4,43]. Tofacitinib has also been effective in improving patient-reported outcomes[35,44,45] and other disease measures that do not incorporate CRP[42]. After reviewing long-term safety and efficacy data, the

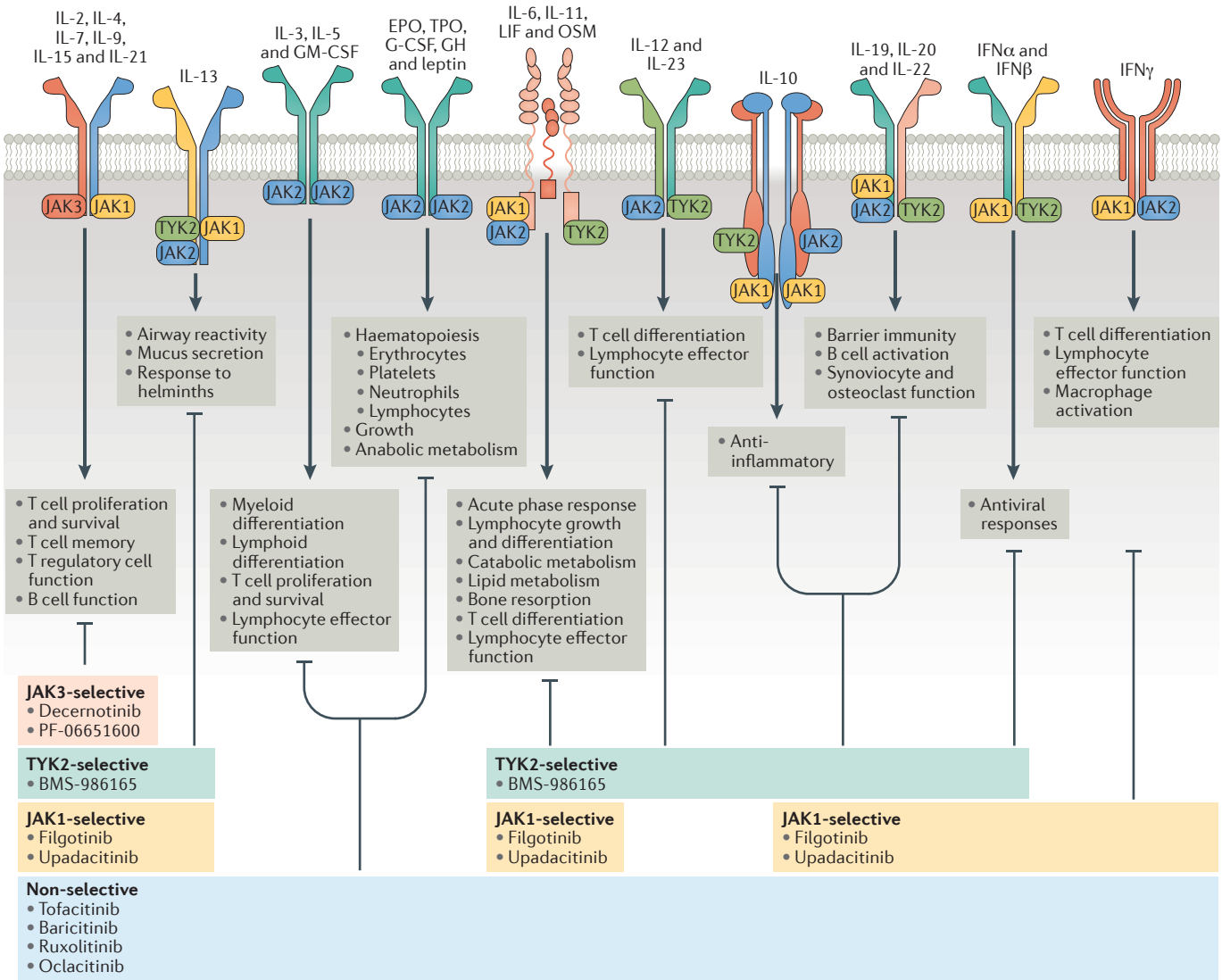

Figure 2 | **Effects of targeting different JAKs.** Type I and type II cytokine receptors physically associate with Janus kinases (JAKs), which transduce downstream intracellular signals. Different receptors associate with different JAKs, so that selective blockade of one JAK can inhibit a specific biologic function while allowing other JAK-dependent cytokines to signal normally. For example, selective blockade of JAK3, which is associated exclusively with the common γ-chain receptor, should inhibit T cell, natural killer (NK) cell and B cell function while leaving haematopoietic and metabolic pathways unaffected. EPO, erythropoietin; granulocyte colony-stimulating factor (G-CSF); GH, growth hormone; GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin; IFN, interferon; LIF, leukaemia inhibitory factor; OSM, oncostatin M; TPO, thrombopoietin; TYK, tyrosine kinase.

36-Item Short Form Survey
(SF-36). A set of generic, coherent and easily administered quality-of-life measures that rely on patient self-reporting and are now widely used by managed care organizations for routine monitoring and assessment of care outcomes in adult patients.

Biologics
Agents that target cytokines or cytokine receptors, usually monoclonal antibodies or chimeric receptors.

Baseline structural damage
Abnormal imaging findings on radiographic assessment, specifically joint space narrowing and erosion.

Complete response letter
A letter issued by the US Food and Drug Administration to communicate that it has completed its review of a drug application and decided not to approve it in its present form.

European Medicines Agency (EMA) also recommended the approval of tofacitinib for rheumatoid arthritis in January 2017. In addition, an extended-release version of tofacitinib that uses osmotic delivery to allow once-daily dosing was approved by the FDA in 2016 for the treatment of rheumatoid arthritis[46].

Baricitinib is a first-generation jakinib that is active against JAK1 and JAK2 (FIG. 3) and is structurally related to ruxolitinib. Baricitinib is cleared by the kidney and is not metabolized via the cytochrome P450 (CYP) system, which sets it apart from tofacitinib and ruxolitinib[47]. It has been studied in the treatment of rheumatoid arthritis, with extensive data from phase III trials that demonstrate its safety and efficacy (TABLE 2). Patients with rheumatoid arthritis refractory to conventional disease-modifying antirheumatic drugs (cDMARDs) displayed clinically significant improvements in disease activity, radiographically assessed structural damage and patient-reported outcomes[48]. Baricitinib was also effective in patients who had not responded to standard-of-care treatment with biologics such as TNF inhibitors, abatacept and tocilizumab[49,50]. In treatment-naive patients, baricitinib outperformed MTX[49,50] and was superior to adalimumab in patients who were refractory to MTX, a previously unseen milestone[51], leading to approval from the EMA for the treatment of rheumatoid arthritis. By contrast, the FDA issued a complete response letter indicating that it was unable to approve the application for baricitinib,

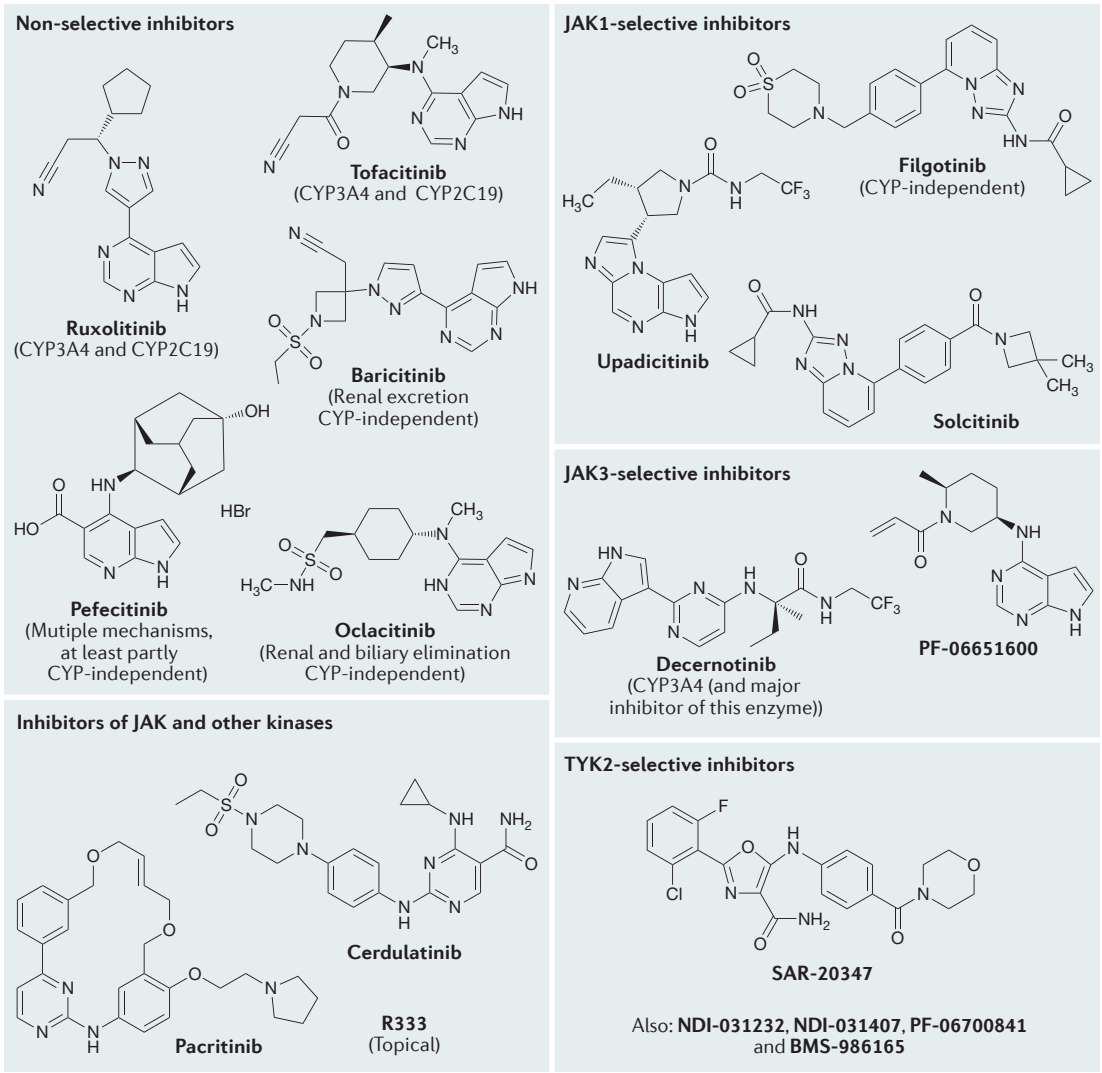

Figure 3 | **Chemical structure and attributes of various jakinibs.** The first-generation Janus kinase (JAK) inhibitors ruxolitinib, tofacitinib and baricitinib block multiple JAKs. The newer pan-jakinib peficitinib has a median inhibitory concentration (IC_{50}) of 3.9, 5.0, 0.71 and 4.8 nmol/L for JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) enzymatic activity, respectively. A variety of next-generation JAK inhibitors are emerging. Several block JAKs and other kinases (R333, cerdulatinib and pacritinib), whereas many are selective for one particular JAK isoform. Filgotinib, upadacitinib and solcitinib block JAK1; decernotinib and PF-06651600 block JAK3; and BMS986165, NDI-021232, NDI-031407, PF-06700841 and SAR-20347 all block TYK2. Chemical structures and data regarding metabolism and/or clearance are shown where available. CYP, cytochrome P450.

Table 1 | **Clinical trials involving tofacitinib**

Study	*n*	Participants	Intervention and efficacy	cDMARD	Other outcome measures	Refs
Rheumatoid arthritis						
ORAL solo	611	Active RA refractory to bDMARD or cDMARD	• Tofacitinib 5 mg b.i.d. (ACR20: 59%) • Tofacitinib 10 mg b.i.d. (ACR20: 65.7%) • Placebo for 3 months (ACR20: 24.4%) followed by tofacitinib 5 mg b.i.d. for 3 months • Placebo for 3 months followed by tofacitinib 10 mg b.i.d. for 3 months	Allowed: antimalarials, prednisone <10 mg daily, NSAIDs	ACR50, ACR70, HAQ-DI, DAS28-ESR, DAS28-CRP, FACIT	34
ORAL step	399	Moderate to severe RA, refractory to TNF inhibitors	• Tofacitinib 5 mg b.i.d. (ACR20: 41.7%) • Tofacitinib 10 mg b.i.d. (ACR20: 48.1%) • Placebo for 3 months (ACR20: 24.4%) followed by tofacitinib 5 mg b.i.d. for 3 months or by tofacitinib 10 mg b.i.d. for 3 months	Required: MTX; allowed: prednisone ≤10 mg daily, NSAIDs	ACR50, ACR70, HAQ-DI, DAS28-ESR, DAS28-CRP, FACIT, SDAI	29
ORAL standard	717	Active RA refractory to MTX	• Tofacitinib 5 mg b.i.d. (ACR20: 51.5%) • Tofacitinib 10 mg b.i.d. (ACR20: 52.6%) • Adalimumab 40 mg biweekly (ACR20: 47.2%) • Placebo for 3 months (ACR20: 28.3%) followed by tofacitinib 5 mg b.i.d. (non-responders) or by tofacitinib 5 mg b.i.d. for 6 months (all) • Placebo for 3 months followed by tofacitinib 10 mg b.i.d. (non-responders) or by tofacitinib 10 mg b.i.d. for 6 months (all)	Required: MTX; allowed: prednisone ≤10 mg daily, NSAIDs	ACR50, ACR70, HAQ-DI, DAS28-ESR; <2.6 other patient-reported outcomes are described in a separate study	30
ORAL sync	792	Active RA, refractory to cDMARD or bDMARD	• Tofacitinib 5 mg b.i.d. for 12 months (ACR20: 52.1%) • Tofacitinib 10 mg b.i.d. for 12 months (ACR20: 56.6%) • Placebo (ACR20: 30.8%) for 6 months followed by tofacitinib 5 mg b.i.d. for 6 months or tofacitinib 10 mg b.i.d. for 6 months	• Required: one cDMARD (no potent immunosuppressives, such as azathioprine or cyclosporin A) • Allowed: prednisone <10 mg daily, NSAIDs	ACR50, ACR70, HAQ-DI, DAS28-ESR, DAS28-CRP	200
ORAL scan	797	Active RA, prior use of bDMARDs or cDMARDs permitted	• Tofacitinib 5 mg b.i.d. for 12 months (ACR20: 51.5%) • Tofacitinib 10 mg b.i.d. for 12 months (ACR20: 61.8%) • Placebo for 3 months (ACR20: 25.3%) followed by tofacitinib 5 mg b.i.d. (non-responders) or by tofacitinib 5 mg b.i.d. for 6 months • Placebo for 3 months followed by tofacitinib 10 mg b.i.d. (non-responders) or by tofacitinib 10 mg b.i.d. for 6 months	• Required: MTX • Allowed: prednisone ≤10 mg daily, NSAIDs	ACR50, ACR70, HAQ-DI, DAS28-ESR, DAS28-CRP, vdH-mTSS, FACIT	38
ORAL start	958	Treatment-naive active RA	• Tofacitinib 5 mg b.i.d. for 6 months (ACR20: 71.3%) • Tofacitinib 10 mg b.i.d. for 6 months (ACR20: 76.1%) • MTX up to 20 mg weekly (ACR20: 50.5%)	Allowed: antimalarials, prednisone <10 mg daily, NSAIDs	ACR50, ACR70, HAQ-DI, DAS28-ESR, DAS28-CRP, vdH-mTSS, FACIT	28
Psoriatic arthritis						
OPAL Beyond	395	Active psoriatic arthritis refractory to TNF inhibitors	• Tofacitinib 5 mg b.i.d. (PASI75: 49.6%) • Tofacitinib 10 mg b.i.d. (PASI75: 47%) • Placebo for 3 months (PASI75: 71.3%) followed by tofacitinib 5 mg b.i.d. for 3 months or by tofacitinib 10 mg b.i.d. for 3 months	Required: one cDMARD	ACR50, ACR70, HAQ-DI, PASI75, DLQI, DSS; 6-month outcomes	201
OPAL Broaden	422	Psoriatic arthritis	• Tofacitinib 5 mg b.i.d. (PASI75: 50.5%) • Tofacitinib 10 mg b.i.d. (ACR20: 60.6%%) • Adalimumab 40 mg biweekly (ACR20: 51.9%) • Placebo for 3 months (PASI75: 33.3%) followed by tofacitinib 5 mg b.i.d. for 9 months or tofacitinib 10 mg b.i.d. for 9 months	Required: one cDMARD	ACR50, ACR70, HAQ-DI, PASI75, DLQI, DSS; 12-month outcomes	N/A
OPAL Balance	817	Psoriatic arthritis	As above	As above	As above	N/A

Table 1 (cont.) | **Clinical trials involving tofacitinib**

Study	*n*	Participants	Intervention and efficacy	cDMARD	Other outcome measures	Refs
Psoriasis						
OPT Pivotal 1 and 2 (two identically designed studies)	1859	Active plaque psoriasis	• Placebo for 16 weeks (PASI75: 6.2% (Pivotal 1), 11.4% (Pivotal 2)) followed by tofacitinib 5 mg or 10 mg b.i.d. • Tofacitinib 5 mg (PASI75: 39.9% (Pivotal 1), 46% (Pivotal 2)) • Tofacitinib 10 mg b.i.d. (PASI75: 59.2% (Pivotal 1), 59.6% (Pivotal 2))	None	PGA 'clear' or 'almost clear', PASI50, PASI90, DLQI, BSA, NAPSI; results at 28 weeks are reported in a separate study	202
OPT Compare	1106	Chronic stable active plaque psoriasis	• Placebo (PASI75: 5.6%) • Etanercept 50 mg twice weekly (PASI75: 58.8%) • Tofacitinib 5 mg b.i.d. (PASI75: 39.5%) • Tofacitinib 10 mg b.i.d. (PASI75: 63.6%)	None	PGA 'clear' or 'almost clear', PASI50, PASI90, BSA, patient-reported itch severity	75
OPT Retreatment	666	Chronic active plaque psoriasis	• Tofacitinib 5 mg (PASI75: 49.9%) • Tofacitinib 10 mg b.i.d. (PASI75: 63.9%) • Tofacitinib 5 mg b.i.d. for 24 weeks followed by withdrawal for 16 weeks (PASI75: 22.9%) • Tofacitinib 10 mg b.i.d. for 24 weeks followed by withdrawal for 16 weeks (PASI75: 18%)	None	PGA 'clear' or 'almost clear', DLQI, PASI50, PASI90	72
OPT Extend	3631	Psoriasis	• As above	None	As above	N/A
Ulcerative colitis						
OCTAVE Induction 1 and 2 (two identically designed studies)	1139	Moderately to severely active ulcerative colitis refractory to corticosteroids, cDMARDs or TNF inhibitors	• Placebo (disease remission: 6.2% (Induction 1), 3.6% (Induction 2)) • Tofacitinib 10 mg b.i.d. (disease remission: 18.5% (Induction 1), 16.6% (Induction 2))	None	Mucosal healing, clinical response	63
OCTAVE Sustain	593	Placebo or tofacitinib-treated patients with clinical response in OCTAVE Induction 1 or 2	• Placebo (disease remission: 11.1%) • Tofacitinib 5 mg (disease remission: 34.3%) • Tofacitinib 10 mg b.i.d. (disease remission: 40.6%)	None	Mucosal healing, clinical response, sustained clinical responses, sustained steroid-free remission	203
OCTAVE Open	1732	All patients in OCTAVE Induction and Sustain trials	As above	None	As above	N/A

ACR20 (50, 70), American College of Rheumatology Criteria 20% (50%, 70%) improvement; bDMARD, biological disease-modifying antirheumatic drug; b.i.d., twice daily; BSA, body surface area involvement; cDMARD, conventional disease-modifying antirheumatic drug; CRP, C-reactive protein; DAS-28, disease activity score based on 28 joints; DLQI, Dermatology Life Quality Index; DSS, dactylitis severity score; ESR, erythrocyte sedimentation rate; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire–Disability Index; MTX, methotrexate; N/A, not applicable; NAPSI, Nail Psoriasis Severity Index; NSAID, nonsteroidal anti-inflammatory drug; PASI75 (50, 90), 75% (50%, 90%) reduction in Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; RA, rheumatoid arthritis; SDAI, Simple Disease Activity Index; TNF, tumour necrosis factor; vdH-mTSS, van der Heijde modified total Sharp score.

citing the need for additional clinical data to determine the most appropriate doses and clarify safety concerns[52]. A resubmission of the new drug application incorporating new safety and efficacy data is planned, with a target date of January 2018 (REF. 53).

Peficitinib is a newer jakinib that also blocks multiple JAKs[54] (FIG. 3). In phase II studies, patients with rheumatoid arthritis treated with peficitinib as monotherapy or in combination with MTX achieved clinical responses similar to those seen with other non-selective jakinibs[54,55,56]. The adverse effects were also largely similar, although anaemia was reportedly not seen in patients treated with peficitinib.

Other forms of arthritis. TNF inhibitors have been effective in the treatment of several other forms of arthritis. However, as in rheumatoid arthritis, they are often not completely effective, and our understanding of the role of various cytokines in other arthritides is very incomplete. Nonetheless, tofacitinib was shown to be effective in the seronegative spondyloarthropathy psoriatic arthritis[57], in which it reduces inflammatory cytokine production by synoviocytes[58]. There was a trend towards higher response rates with tofacitinib than with the standard-of-care TNF inhibitor adalimumab, but the phase III trial that compared the two treatments was not adequately powered to assess superiority. In 2017, the FDA Advisory Committee recommended approval of tofacitinib for psoriatic joint disease. Tofacitinib also demonstrated efficacy in ankylosing spondylitis, another seronegative spondyloarthropathy[59,60]. The efficacy of tofacitinib in seronegative spondyloarthropathy represents a potentially important advance, as the therapeutic armamentarium for this group of diseases comprises only three FDA-approved

Table 2 | **Rheumatoid arthritis clinical trials involving baricitinib**

Study name	*n*	Participants	Intervention	Concomitant DMARDs	Study duration	Efficacy (ACR20)	Other outcome measures	Refs
RA-BEACON	527	Active RA refractory to bDMARDs	• Baricitinib 2 mg daily • Baricitinib 4 mg daily • Placebo	Allowed: cDMARDs, NSAIDs, prednisone ≥10 mg daily	24 weeks (outcomes reported at 12 weeks)	• Placebo: 27% • Baricitinib 2 mg: 49% • Baricitinib 4 mg: 55%	ACR50, ACR70, HAQ-DI, DAS28-ESR, DAS28-CRP, CDAI, SDAI	50
RA-BUILD	684	Active RA refractory to cDMARDs (prior bDMARDs not allowed)	• Baricitinib 2 mg daily • Baricitinib 4 mg daily • Placebo	Allowed: up to 2 cDMARDs, NSAIDs, prednisone ≥10 mg daily	24 weeks	• Placebo: 39% • Baricitinib 2 mg: 66% • Baricitinib 4 mg: 62%	ACR50, ACR70, HAQ-DI, DAS28-ESR, DAS28-CRP, CDAI, SDAI, MJS duration and severity, vdH-mTSS	48
RA-BEGIN	584	Active RA, DMARD-naive (≤3 doses of MTX allowed)	• Baricitinib 4 mg daily • Baricitinib 4 mg daily + MTX • MTX	Required: MTX (if assigned) Allowed: NSAIDs, prednisone >10 mg daily	52 weeks (outcomes reported at 24 weeks)	• MTX: 62% • Baricitinib 4 mg: 77% • Baricitinib + MTX: 78%	ACR50, ACR70, HAQ-DI, DAS28-ESR, DAS28-CRP, CDAI, SDAI, vdH-mTSS	49
RA-BEAM	1305	Active RA on stable background MTX	• Placebo • Baricitinib 4 mg daily • Adalimumab 40 mg biweekly	Required: MTX Allowed: NSAIDs, prednisone >10 mg daily	24 weeks (outcomes reported at 12 weeks)	• Placebo: 40% • Adalimumab: 61% • Baricitinib 4 mg: 70%	ACR50, ACR70, HAQ-DI, DAS28-ESR, DAS28-CRP, CDAI, SDAI, MJS duration and severity, vdH-mTSS	51

ACR20 (50, 70), American College of Rheumatology Criteria 20% (50%, 70%) improvement; bDMARD, biological disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; cDMARD, conventional disease-modifying antirheumatic drug; CRP, C-reactive protein; DAS28, disease activity score based on 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire–Disability Index; MJS, morning joint stiffness; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; SDAI, Simple Disease Activity Index; vdH-mTSS, van der Heijde modified total Sharp score.

classes of drugs: TNF inhibitors, ustekinumab and the IL-17 blocking agent secukinumab. Tofacitinib is also being evaluated for the treatment of juvenile idiopathic arthritis (NCT01500551, NCT02592434), as it was reported effective in an adult patient with long-standing treatment-refractory polyarticular disease[61].

Inflammatory bowel disease

IBD is a term that encompasses two diseases, ulcerative colitis and Crohn's disease, but more likely represents a broad constellation of inflammatory disorders of the gastrointestinal tract driven by multiple diverse mechanisms that affect tissues beyond the gut, including joints. Ulcerative colitis is typically restricted to the colon and primarily affects the mucosa, whereas Crohn's disease is characterized by transmural inflammation, skip lesions and inflammation throughout the gastrointestinal tract; however, there can be considerable overlap between the two diseases. Despite the success of biologics including TNF blockers, ustekinumab and vedolizumab (an $\alpha_4\beta_7$ integrin inhibitor), current IBD therapies are ineffective for many patients. Tofacitinib 10 mg b.i.d. has proved an effective induction treatment for both moderate and severe ulcerative colitis in phase III studies, inducing remission in 16–18% of patients and mucosal healing in 28–31%[62]. Another phase III trial has demonstrated that two doses of tofacitinib (5 mg and 10 mg) are effective in maintaining remission of ulcerative colitis for up to 1 year[62]. Consequently, the FDA has accepted a supplemental new drug application for tofacitinib in moderate to severe ulcerative colitis. Results in Crohn's disease have been less consistent[63], with 2017 data suggesting a very modest treatment effect for both induction and maintenance therapy compared with placebo[64]. The basis for differences in efficacy between these two conditions is unknown, but it could relate to the basic mechanism of disease and differential contribution of various JAK-dependent cytokines to immunopathogenesis. JAK-dependent cytokines such as IL-6 are generally implicated in IBD pathogenesis; however, IL-9 is thought to be involved in the pathogenesis of ulcerative colitis but not in that of Crohn's disease[65]. Moreover, the JAK-dependent cytokine IL-10 has critical anti-inflammatory effects in the gut; therefore, blockade with jakinibs has the potential to be detrimental to patients with IBD. Impaired barrier function, dysbiosis and bacterial overgrowth are integral to the pathogenesis of IBD. The type I and type II cytokines IL-9 and IL-22, respectively, are important for maintaining barrier integrity[66,67], underlying another potential mechanism by which jakinibs could be detrimental in IBD. IL-17, also important for gut barrier function, does not signal via JAKs but is regulated by IL-6 and IL-23, which are JAK-dependent. In the case of IL-17, clinical trials using IL-17A-blocking antibodies to treat IBD showed unexpected disease exacerbation, possibly due to loss of mucosal protection[68,69]. It is also possible that immunodeficiency underlies some forms of IBD, and thus the disease could be exacerbated by jakinibs[70]. Further data from late-phase clinical trials and a more sophisticated understanding of IBD pathogenesis should help to clarify these concerns and identify the best candidates for treatment with jakinibs.

Transmural inflammation
Full-thickness inflammation across the entire bowel wall (as opposed to being limited to the mucosa and submucosa).

Skip lesions
Lesions that are discontinuous. In the context of this Review, the term refers to discontinuous lesions in the gastrointestinal tract.

Dermatologic conditions

Psoriasis. Psoriasis is an autoimmune skin disorder responsive to the inhibition of multiple cytokines including TNF, IL-17, IL-12 and IL-23 and IL-23 separately. Given the JAK dependence of multiple cytokines involved in the pathogenesis of psoriasis, tofacitinib has been tested extensively in late-phase clinical trials for the treatment of this disease. Patients treated with tofacitinib experienced clinically significant improvements according to the Psoriasis Area and Severity Index 50%, 75% and 90% improvement criteria (PASI50, 75 and 90) at doses of both 5 mg and 10 mg b.i.d.[71,72] (TABLE 1). Tofacitinib rapidly blocked STAT phosphorylation in keratinocytes from patients with psoriasis and abrogated keratinocyte-induced pathogenic cytokine signalling, both of which may underlie its efficacy[73]. However, in a trial that compared tofacitinib with standard-of-care treatment with the TNF inhibitor etanercept, only the 10 mg b.i.d. dose of tofacitinib showed non-inferiority[74]. The FDA issued a complete response letter indicating that it would not be able to approve tofacitinib for psoriasis without additional information[75] that could establish the appropriate safety:benefit ratio of the 10 mg b.i.d. dose. Additional data from long-term extension studies establishing the safety profile of tofacitinib have emerged over the past 2 years and may influence future decisions regarding FDA or EMA approval, as may the approval of the IL-17-blocking agents secukinumab and ixekizumab and their relative safety and efficacy in psoriatic skin disease.

Baricitinib was also found to be efficacious in a phase II study testing its effect in patients with moderate to severe psoriasis, with over 50% of patients achieving a sustained response as measured by the PASI75 (REF. 76) (TABLE 2). These responses were also seen predominantly at the higher daily doses of 8 mg and 10 mg, although baricitinib has not been compared with TNF inhibitors.

Peficitinib was also reported to be effective for psoriasis in a phase II trial[77], although no phase III trials are currently recruiting patients.

Considering the adverse effects reported with systemic drugs, topical formulations are an attractive alternative for cutaneous disease. Topical formulations of tofacitinib and ruxolitinib have been developed and tested against psoriasis in phase II studies, and treatment with topical tofacitinib demonstrated a significantly higher response rate at 8 weeks than placebo, but the efficacy was transient and was no longer present at the 12-week trial end point[78]. Trials with topical ruxolitinib demonstrated improvement in psoriasis compared with placebo or other topical approved therapies, but as with tofacitinib, the improvement was not sustained after discontinuation[79,80]. Importantly, systemic absorption was minimal and there was no evidence of systemic toxicity[80].

Alopecia areata. Alopecia areata is an autoimmune disorder in which hair follicles overexpress a variety of pro-inflammatory cytokines[81]. Several case reports have been published using jakinibs to treat alopecia areata (affecting localized areas of the scalp), alopecia totalis (affecting the entire scalp) and alopecia universalis (affecting the entire body)[10]. Moreover, alopecia areata is characterized by tissue upregulation of genes induced by IFNγ, which signals through JAK1 and JAK2 (REFS 1,82). Early-phase clinical trials and large retrospective studies indicate that tofacitinib[83–86], ruxolitinib and baricitinib[87,88] are effective for the spectrum of autoimmune forms of alopecia. However, symptoms recur upon drug discontinuation[89], and tofacitinib may lose efficacy in some patients[90]. Topical ruxolitinib has also demonstrated efficacy in treatment of alopecia areata[91], and there is an ongoing clinical trial evaluating the efficacy of topical tofacitinib (NCT02812342). Of considerable interest, it also seems that JAK inhibition can promote hair regrowth, which will likely attract more investigation[84].

Atopic dermatitis. Atopic dermatitis, also known as atopic eczema, is a common disorder in which cytokines associated with allergic disease (such as IL-4, IL-5 and IL-13) are frequently overexpressed. The pathogenic role of cytokines is evidenced by the utility of biologics targeting these cytokines. Oclacitinib (FIG. 3) is the first jakinib to gain FDA approval for allergic and atopic canine dermatitis[92,93], which provides a strong precedent for the use of jakinibs to treat atopic dermatitis in humans, and preclinical studies indicate that this strategy would likely be effective[94,95]. Inflammation in atopic dermatitis is often complicated by concomitant irritant contact disease, a disease in which JAK-dependent cytokines such as IL-6 and IL-31 have an important role[96] and in which JAK2 inhibitors may reduce pathology[97]. A clinical trial using baricitinib to treat atopic dermatitis is ongoing (NCT02576938). Balancing efficacy and safety is always a priority, especially in this disease, in which morbidity might be high but mortality is low; therefore, topical formulations of jakinibs are desirable if efficacious[98]. Tofacitinib ointment is efficacious in the treatment of atopic dermatitis, with an 80% improvement in Eczema Area and Severity Index (EASI) scores after 4 weeks of treatment[99]. One prominent feature of atopic dermatitis is pruritus, which results in an itch–scratch cycle. Cytokines have also been linked to the molecular pathogenesis of pruritus, such that treating with jakinibs might break the itch–scratch cycle[100].

Other dermatologic conditions. Tofacitinib has been reported efficacious in the treatment of vitiligo[101], and a clinical trial using topical ruxolitinib for this indication is ongoing (NCT02809976). Palmoplantar pustulosis[102], a refractory form of psoriatic skin disease that can be associated with arthritis, has also been treated successfully with tofacitinib. Finally, a case of the mucocutaneous disease idiopathic erythema multiforme associated with a mutation in *TRPS1* and JAK–STAT activation was treated successfully with tofacitinib[103]. It would be intriguing to see whether other dermatologic diseases might be similarly responsive to jakinibs: candidates would include mycosis fungoides, graft-versus-host disease (GVHD) and cutaneous lupus.

Psoriasis Activity and Severity Index
A standardized score used to measure the severity and extent of skin involvement in psoriasis. A representative area of psoriasis is selected for each body region, and the intensity of redness, thickness and scaliness is assessed on a scale of 0 (none) to 4 (very severe).

Other autoimmune diseases

Transplant rejection results from recognition and destruction of allogeneic organs by host immune cells[104]. Tofacitinib was first studied in the prevention of transplant rejection[105,106], in which it was efficacious but was also associated with an unacceptable risk of adverse events due to over-immunosuppression. Foremost among these were BK viraemia, nephropathy and post-transplant lymphoproliferative disease (PTLD). This risk may be due to the relatively high doses of tofacitinib used in the transplant trials (10–15 mg b.i.d.) and to the treatment of the transplant patients with other potent immunomodulatory drugs (basiliximab, mycophenolate or sirolimus) at the same time. Measuring post-dose serum concentrations to prevent overexposure may prevent such outcomes and lead jakinibs to be re-evaluated for the prevention of transplant rejection[107].

Baricitinib has been used in the treatment of autoinflammatory diseases, particularly those characterized by an IFN signature, or activation of IFN signalling genes[108]. The doses required have been high (mean dose 8.5 mg/day), and treatment has been associated with BK viraemia[108,109], possibly owing to the over-immunosuppression required to control symptoms.

Jakinibs are also being used to treat other diseases associated with an IFN signature, namely, systemic lupus erythematosus (SLE), dermatomyositis and Sjogren's syndrome. For SLE, preclinical studies have been encouraging[110]. A phase I trial of tofacitinib (NCT02535689) and a phase II study of baricitinib (NCT02708095) are currently recruiting patients. Several cases of jakinib-responsive myositis[111–113] have also been reported, and a clinical trial is planned (NCT03002649), although recruitment has not yet started.

Dry eye disease is a clinically heterogeneous group of disorders, a subset of which is caused by immune-mediated pathologies, including the autoimmune disease Sjogren's syndrome[114]. Topical ophthalmic tofacitinib has been tested in the treatment of dry eye disease, in which results showed a trend towards improvement but were not significantly different from placebo[115]. It should be noted that patient selection may have contributed to the lack of efficacy: dry eye disease is not always caused by immune-mediated mechanisms[114], and patient responses to topical cyclosporine, which is FDA-approved for keratoconjunctivitis sicca and served as the positive control for the study, were also poor[115].

Given the number of immune-mediated diseases linked to activation of JAK-dependent cytokines, jakinibs are also being investigated for a host of other indications. Secondary hypereosinophilic syndrome (HES)[98] is a group of disorders characterized by elevation of JAK-dependent cytokines including IL-4, IL-5 and IL-13. The IL-5 blocking agent mepolizumab is extremely effective in the treatment of HES[116] and other eosinophilic diseases including allergic asthma[6], although some patients fail to respond completely, raising the possibility that blockade of multiple JAK-dependent cytokines might increase therapeutic efficacy. Preliminary reports support the efficacy of jakinibs in treating HES[98], indicating that jakinibs might be useful in other diseases driven by the same cytokines, such as eosinophilic oesophagitis and allergic asthma.

Tofacitinib has been reported as a treatment for vasculitis[117] and has shown promising results in preclinical models[118] of GVHD: a clinical trial of baricitinib for this indication is ongoing (NCT02759731). Another potential use could be another major autoimmune disease, multiple sclerosis, a disease driven by diverse cytokines[119]. In principle, tofacitinib could be useful in antagonizing pathogenic cytokines; however, IFNβ is an approved treatment for this disease. Thus, it remains to be seen whether jakinibs will be useful in multiple sclerosis.

Other diseases

The role of JAK-dependent cytokines is increasingly being appreciated in several common diseases traditionally seen as driven by non-immunologic mechanisms. For example, preliminary data suggest that tofacitinib is a potential treatment for diabetic nephropathy, in which it seems to reduce albuminuria through blockade of renal inflammation[120]. Another such example is cardiovascular disease (CVD), which is increasingly being seen as an inflammatory process[121]. Among other cytokines, IL-6 is associated with the pathogenesis of CVD[122], and the JAK–STAT pathway has been proposed as a potential therapeutic target in atherosclerosis[123].

The downside of JAK inhibition

The adverse effects of jakinibs are largely predictable based on their biological functions as signal transducers for type I and type II cytokines. Because tofacitinib is the most widely used jakinib, its safety profile is the best characterized. However, the side effects of baricitinib and other non-selective jakinibs are similar, which is expected given the similar cytokine inhibition of the two drugs[124].

Infection. It is not surprising that the greatest concerns regarding adverse effects have focused on the increased risk of infection. Indeed, an analysis of several rheumatoid arthritis trials revealed that infections were commonly reported side effects[24–26,31,33,125]. Although most infections did not necessitate treatment discontinuation, there were also reports of some severe and opportunistic infections such as tuberculosis and osteomyelitis that did necessitate treatment discontinuation. However, the risk of serious infections for jakinibs seem to be similar to that seen with biological agents[31], and jakinibs may be less likely to increase infection risk[31,125]. Tofacitinib, baricitinib and peficitinib are associated with increased risk of herpes zoster infection, and other more serious viral infections have been associated with jakinibs, including a case of progressive multifocal leukoencephalopathy secondary to John Cunningham virus, associated with ruxolitinib[126]. BK nephropathy has also been reported in trials that evaluated the use of tofacitinib in preventing rejection after kidney transplantation, in combination with mycophenolate mofetil or cyclosporine[105,106]. Inhibition of IFN signalling and depletion of natural killer (NK) cells may underlie the increased risk of viral infection. NK cells are critical for

BK viraemia
Disseminated viral infection with BK virus, a polyomavirus whose name is an abbreviation of the name of the index patient from whom this virus was isolated.

Post-transplant lymphoproliferative disease
(PTLD). A post-transplantation malignancy that can occur as a complication of solid organ or haematopoietic stem cell transplantation. Often associated with Epstein-Barr virus infection of B cells.

Sjogren's syndrome
A systemic autoimmune condition characterized by autoimmune exocrinopathy (salivary and lacrimal glands), as well as, in some cases, systemic inflammation (central nervous system, hepatic, skin, renal and others).

Myositis
Inflammation of the muscles. In the context of this Review, myositis refers to the two systemic autoimmune conditions polymyositis and dermatomyositis.

Eosinophilic oesophagitis
A disease characterized by eosinophilic inflammation of the oesophagus, also termed allergic oesophagitis.

antiviral defence, and their development and function both depend on JAK3-dependent cytokines. Tofacitinib causes a dose-dependent decrease in NK cell count, although this effect may be temporary[127,128], and careful studies that probe tofacitinib-mediated alterations in NK cell function are needed. Tofacitinib may also affect the development and function of plasmablasts[129], also important in host defence against viral infection[130]. Tofacitinib does not affect response to influenza vaccination but decreases response to pneumococcal vaccination, particularly in combination with MTX, and temporary withdrawal does not restore responsiveness[131]. Thus, patients should be vaccinated against herpes zoster and pneumococcal infections prior to starting tofacitinib, as with other biological disease-modifying antirheumatic drugs (bDMARDs)[132–134].

Anaemia and leukopenia. Because haematopoietic growth factors — including erythropoietin — signal through JAK2, cytopenias are commonly seen in patients treated with first-generation pan-jakinibs. Neutropenia and anaemia have been observed in many trials of patients with rheumatoid arthritis, particularly at higher doses of tofacitinib[24–26,40,105]. These alterations were typically well tolerated and did not require treatment discontinuation. Anaemia and neutropenia were also reported in patients treated with baricitinib[48,49,50,135]. Patients treated with peficitinib developed neutropenia but did not develop anaemia; instead, increases in haemoglobin were noted at higher doses of the drug, which may reflect resolution of inflammation-driven anaemia of chronic disease. Unexpectedly, mild thrombocytosis was noted in patients treated with baricitinib, although not in those treated with tofacitinib. Because JAK2 blockade is an FDA-approved treatment for essential thrombocytosis[10], one would instead expect thrombocytopenia as an adverse effect, and the causes underlying treatment-associated thrombocytosis are not clear.

Lipids and cardiovascular disease. Patients with autoimmune diseases, including rheumatoid arthritis and SLE, are at increased risk of CVD, a major cause of mortality[136–137] in these patients. Patients with psoriasis are also at risk of CVD[138] and metabolic syndrome, more so than patients with other inflammatory diseases[129,136,139]. The reasons for this risk are likely multifactorial: patients with autoimmune disease have a high prevalence of cardiovascular risk factors and autoimmune disease activity also increases the risk of CVD[126, 136,138,139–141]. JAK-dependent cytokines are thought to contribute to CVD in autoimmunity, implying that JAK inhibition may actually reduce this risk. Type I IFNs promote endothelial dysfunction[142], whereas IL-6 affects lipid metabolism, drives insulin resistance and promotes redistribution of serum lipids to peripheral tissues. This redistribution of lipids causes a decrease in serum lipid levels, which may paradoxically raise the risk of CVD by increasing the deposition of lipids in vascular tissue[143,144]. Indeed, patients treated with the IL-6R inhibitor tocilizumab have increased levels of lipids in their serum but do not seem to have an increased risk of CVD[145].

Potentially related to blockade of signalling downstream of IL-6, treatment with non-selective jakinibs also increases levels of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) in serum but does not alter the LDL:HDL ratio[146]. Review of pooled data from late-phase clinical trials indicates that tofacitinib, like tocilizumab, does not increase the risk of major cardiovascular events[147,148]. However, patients with CVD were excluded from the late-phase clinical trials, limiting the generalizability of this finding[147]. Moreover, tofacitinib reduces cholesterol ester catabolism, which is elevated in patients with rheumatoid arthritis[149]. Tofacitinib also reduces arterial stiffness[150] and lupus-associated vascular dysfunction[110]. Long-term data from phase IV clinical trials are needed to determine whether JAK inhibition ultimately eliminates, ameliorates or exacerbates the risk of CVD. Clearly, additional work in this area is warranted.

Gastrointestinal perforation. Patients treated with IL-6R inhibitors also have a higher risk of perforation of the lower gastrointestinal tract than patients treated with other bDMARDs[151], raising the concern that jakinibs may cause similar complications. Although lower gastrointestinal tract perforation was reported in several clinical trials assessing tofacitinib in patients with rheumatoid arthritis, thus far, no significantly increased risk has been seen in analysis of late-phase clinical trial data or in the phase III trials evaluating baricitinib[68]. The mechanisms by which jakinibs might increase the risk of lower gastrointestinal tract perforation are poorly defined but may be tied to the role of cytokines in gut barrier immunity, including IL-22, IL-10 and IL-9 (REFS 152,153). The association of jakinibs with lower gastrointestinal tract perforation highlights the multifaceted role of JAK-dependent cytokines in immune homeostasis and the importance of long-term monitoring for unexpected complications.

Cancer. Aside from infection, one concern with immunosuppression is the potential for increased risk of malignancy. The possible mechanisms through which jakinibs might inhibit immune responses to cancer include interference with T and NK cell function in immunosurveillance and with the antineoplastic role of IFNs. In patients receiving tofacitinib after kidney transplantation, the risk of post-transplant lymphoproliferative disorder is indeed elevated[106]. Thus far, data from clinical trials and long-term extension studies in patients with rheumatoid arthritis have not revealed an increased risk of haematological malignancies or solid tumours[154]. Further monitoring of patients treated with tofacitinib will be needed to determine whether long-term therapy confers any risk of cancer.

Other side effects of jakinibs. Other side effects in patients treated with jakinibs include sporadic elevations in serum creatinine[155], although these levels usually return to baseline upon drug discontination[31,40,155]. Acute renal failure was infrequent and associated with concurrent serious illness, primarily infection[156]; chronic

Plasmablasts
Immature cells of plasma cell lineage, a type of B cell. Plasmablasts secrete more antibodies than B cells but fewer than mature plasma cells.

renal dysfunction has not been reported as an adverse effect of jakinibs[31,40,155]. Some jakinibs have also been reported to cause elevations in levels of transaminases [127]. This effect is more common in patients being treated with tofacitinib and MTX in combination and may necessitate dose adjustment or discontinuation[34]. In tofacitinib-treated rats, prolonged blockade of JAK2 downstream of prolactin causes testicular Leydig cell hyperplasia and adenoma[157]. Because human Leydig cells are not prolactin dependent[157], tofacitinib is not likely to cause testicular adenomas in patients. However, other long-term risks of hormone-like receptor blockade may become apparent from long-term extension studies.

Next-generation jakinibs

Non-selective JAK inhibitors have already been proved safe and efficacious; however, the generation of selective jakinibs with a narrow spectrum of action on cytokines could, in principle, maintain efficacy and improve safety (TABLES 3,4). Moreover, novel mechanisms of achieving high selectivity are emerging. All current jakinibs act on JAKs through non-covalent interactions with the kinase domain, which is relatively conserved between isoforms, but several novel compounds have been reported to bind covalently to non-conserved amino acid residues, leading to irreversible inhibition and reportedly high selectivity across the kinome. It is important, however, to appreciate that specificity as defined by doses used *in vitro* and in cell-based assays may lead to different conclusions compared with specificity as measured in patients treated with doses required for clinical efficacy.

JAK1-selective inhibitors. Filgotinib (FIG. 3) is a JAK1-selective inhibitor with reduced activity against JAK2 (REF. 158). Filgotinib was discovered after a kinase-focused high-throughput library screen identified triazolopyridines as JAK1-selective catalytic inhibitors; this strategy has since been exploited to develop most of the other patented JAK1-selective drugs[159,160,161]. Further structure–activity relationships and structure-based drug design culminated in the development of filgotinib, which was effective in mouse models of inflammatory diseases such as arthritis and colitis[159]. Filgotinib was subsequently investigated in rheumatoid arthritis as monotherapy and in combination with MTX for patients with inadequate responses to MTX[162]. In both settings, filgotinib displayed comparable efficacy to tofacitinib. Importantly, with respect to the purported lack of effect on JAK2, patients did not develop anaemia; rather, a mild increase in haemoglobin was observed. However, patients did develop neutropenia, possibly due to inhibition of cytokines such as G-CSF and IL-11, which signal through JAK1 and support myelopoiesis[162]. Other laboratory abnormalities were similar to those seen with tofacitinib, with dose-dependent increases in serum transaminases and lipids. Unlike tofacitinib, however, filgotinib increased the HDL/LDL ratio. Filgotinib is also the first jakinib to display clinically significant efficacy in Crohn's disease[163], with a twofold increase in clinical remission compared with placebo and remission rates similar to those seen with the standard-of-care therapy infliximab. Phase III trials are currently ongoing for both ulcerative colitis and Crohn's disease (NCT02914561 and NCT02914522).

Upadacitinib (FIG. 3) was developed by using structural predictions that indicated potential for differential binding interactions outside the ATP binding between JAK1 and JAK2, which is believed to provide JAK selectivity via an allosteric mechanism[164,165]. The efficacy of upadacitinib in rheumatoid arthritis was evaluated in the BALANCE1 and two phase II clinical trials[166,167], in which patients who did not respond to either MTX or TNF inhibitors were treated with upadacitinib in combination with MTX. ACR20 responses were similar to those seen with non-selective jakinibs such as tofacitinib, and results were seen as early as 2 weeks after the start of treatment. Adverse effects included infection, transient increase in levels of serum transaminases and dose-dependent increases in serum lipid levels. Dose-dependent decreases in levels of haemoglobin were noted in patients treated with upadacitinib, raising the possibility that at the higher doses needed to control autoimmune disease, the drug does inhibit JAK2 (REFS 166,167) or that JAK1-dependent cytokines are necessary for normal erythropoiesis. Upadacitinib is metabolized by CYP enzymes including CYP3A but can be taken with other CYP3A-metabolized drugs, including statins[168,169], which may be relevant in terms of the effects of jakinibs on lipid transport. Results from the phase III SELECT programme have been encouraging in patients with rheumatoid arthritis who are refractory to cDMARDs; further trials are evaluating the drug in treatment-naive patients and in patients who are refractory to MTX and bDMARDs[170]. Positive results, including increased rates of clinical and endoscopic remission, have also emerged from the CELEST trial in Crohn's disease[171], and trials are ongoing for atopic dermatitis (NCT02782663, NCT02925117 and NCT02819635).

Solcitinib (GLPG-0778 and GSK-2586184) (FIG. 3) is a JAK1-selective inhibitor that has a triazolopyridine scaffold and a cyclopropylamide in position two and was derived from GLPG0634 (which was originally discovered using high-throughput screening). Solcitinib was found to be efficacious for the treatment of plaque psoriasis[172]. However, during a phase II trial that evaluated solcitinib as a treatment for SLE, six patients developed elevated liver enzymes, two of whom were diagnosed with drug reaction with eosinophilia and systemic symptoms[173]. The trial was terminated early on account of these severe adverse events, and the subsequent discovery of a statin drug–drug interaction led to discontinuation of further development of the drug. PF-04965842 is another next-generation JAK1-selective drug; although clinical trials for SLE and plaque psoriasis were discontinued owing to changes in the drug development portfolio, a phase II trial for the treatment of atopic dermatitis is currently under way (NCT02780167).

Table 3 | **Jakinibs that are FDA approved or in or past phase II clinical trials**

Drug	Target	Status	Diseases	Clinical trial identifier
Ruxolitinib (INC424)	JAK1, JAK2	FDA and EMA approved	Myeloproliferative neoplasms	N/A
		Phases II, III	Various cancers	NCT02117479, NCT00638378, NCT01562873, NCT00639002, NCT02723994, NCT02119676, NCT02876302, NCT01712659, others
		Phases II, III	GVHD	NCT02913261, NCT02953678, NCT02396628
		Phase II	RA	NCT00550043
		Phase II	AA	NCT01950780
		Phase II	Vitiligo, AA, psoriasis, AD (topical)	NCT02809976, NCT00617994, NCT02553330, NCT03011892
Tofacitinib (CP690550)	JAK3>JAK1>>(JAK2)	FDA approved, EMA approval recommended	RA	N/A
		FDA approval recommended	Psoriasis and psoriatic arthritis, UC, juvenile idiopathic arthritis,	NCT02592434, NCT01500551, NCT01976364, NCT03000439, NCT01470612, NCT01882439, NCT01877668
		Phase II	AA, Crohn's disease, ankylosing spondylitis, kidney transplant	NCT01786668, NCT01393899, NCT01393626, NCT01470599, NCT00615199, NCT02299297, NCT02197455, NCT02312882, NCT01375127, NCT00106639, NCT00263328, NCT00483756, NCT00658359
		Phase II	Psoriasis, AA, AD (topical)	NCT02001181, NCT02812342, NCT02193815, NCT00678561, NCT01831466, NCT01246583
Oclacitinib	JAK1	FDA approved	Canine allergic dermatitis	N/A
Baricitinib (INCB28050, LY3009104)	JAK1, JAK2	EMA approved	RA	N/A
		Phase II	GVHD, giant cell arteritis, diabetic nephropathy	NCT02759731, NCT03026504, NCT01683409
Decernotinib (VX509)	JAK3	Phases II, III	RA	NCT01830985, NCT01590459, NCT01052194
Upadacitinib (ABT494)	JAK1	Phase III	RA	NCT02955212, NCT02706847, NCT02720523, NCT02629159, NCT02706873, NCT02675426, NCT02706951, NCT02049138
		Phases II, III	UC, Crohn's disease	NCT03006068, NCT02782663, NCT02819635, NCT02365649
		Phase II	AD	NCT02925117
Filgotinib (GLPG0634)	JAK1	Phase III	RA	NCT02873936, NCT03025308, NCT02886728, NCT02889796, NCT02885181
		Phases II, III	UC, Crohn's disease	NCT02048618, NCT02914600, NCT02914535, NCT03077412, NCT03046056, NCT02914561, NCT02914522
Itacitinib (INCB039110)	JAK1, JAK2	Phase II	Psoriasis, RA, pruritus	NCT01634087, NCT01626573, NCT02909569
Peficitinib (ASP015K)	Pan-JAK	Phase III	RA	NCT01638013
R333*	JAK, SYK	Phase II	Discoid lupus erythematosus	NCT01597050
PF-06651600	JAK3	Phase II	RA, AA, UC	NCT02969044, NCT02974868, NCT02958865
PF-06700841	JAK1, TYK2	Phase II	Psoriasis, AA, UC	NCT02969018, NCT02974868, NCT02958865
BMS-986165	TYK2	Phase II	Psoriasis	NCT02534636, NCT02931838
Solcitinib (GSK2586184, GLG0778)*	JAK1	Phase II, phase I	Psoriasis, SLE	NCT02000453, NCT01782664, NCT01687309, NCT01777256, NCT01953835
PF-04965842 *	JAK1	Phase II	Psoriasis, AD	NCT02201524, NCT02780167

AA, alopecia areata; AD, atopic dermatitis; EMA, European Medicines Agency; FDA, US Food and Drug Administration; GVHD, graft-versus-host disease; JAK, Janus kinase; N/A, not applicable; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SYK, tyrosine-protein kinase SYK; TYK, tyrosine kinase; UC, ulcerative colitis. *Further development has been discontinued.

Table 4 | **Jakinibs under early investigation (discontinued compounds are excluded)**

Drug	Target	Status	Diseases	Clinical trial identifier
SAR-20347	JAK1, TYK2	Preclinical	Psoriasis	N/A
Cerdulatinib (PRT-062070)	Pan-jakinib, SYK	Preclinical	Collagen-induced arthritis	N/A
NDI-031407	TYK2	Preclinical	Inflammatory bowel disease, psoriasis	N/A
NDI-031232	TYK2	Preclinical	Response to IL-12	N/A
SHR-0302	Pan-jakinib	Phase I	Rheumatoid arthritis	NCT02892370, NCT02665910
VR588	Pan-jakinib	Early phase I	Severe asthma	NCT02740049
SB-1578	JAK2, FLT3, c-FMS	Phase I	Healthy subjects	NCT01235871
JTE-052	Non-selective	Phase I	Atopic dermatitis	JapicCTI-152887, JapicCTI-142494

c-FMS, macrophage colony-stimulating factor 1 receptor; FLT3, receptor-type tyrosine-protein kinase FLT3; JAK, Janus kinase; N/A, not applicable; SYK, tyrosine-protein kinase SYK; TYK, tyrosine kinase.

JAK3-selective inhibitors. Decernotinib (FIG. 3) is reported to be a JAK3-selective inhibitor developed to preserve JAK1 and JAK2 signalling, which, in principle, would eliminate non-immunological adverse effects. This profile is expected because JAK3 transmits signals via common γ-chain-associated cytokines, which mainly affect immune cells[12,13] (FIG. 2). However, *in vitro* assays indicate that decernotinib may have some activity against JAK1, and the drug has been reported to cause neutropenia in clinical trials[174,175,176]. Therefore, the degree of JAK3 selectivity has yet to be fully determined.

Decernotinib was discovered by using high-throughput screening of a compound library *in vitro*[177]. It has comparable efficacy to tofacitinib for rheumatoid arthritis in phase II trials, both as monotherapy and in combination with MTX[175,176,178]. These results were encouraging, but the development of neutropenia in patients treated with decernotinib was puzzling. Another major concern arises from the fact that decernotinib alone among the JAK inhibitors is a potent inhibitor of CYP3A4 (REF. 179). Because CYP3A4 is the predominant hepatic CYP, it metabolizes over half of the medications currently used to treat human disease, including high-potency statins. This drug–drug interaction could present a limitation to decernotinib use.

Several novel compounds are reported to bind covalently to non-conserved amino acid residues, leading to irreversible inhibition and reportedly high selectivity across the kinome[180]. Because both of these features are new, it will be critical to carefully assess the risks and benefits of each of those compounds as they proceed to clinical development and to assess whether the reported *in vitro* selectivity translates to *in vivo* efficacy and selectivity. PF-06651600 is the only irreversible covalent JAK3 inhibitor being used in clinical trials; it was developed by modifying the structure of tofacitinib to optimize selectivity and allow covalent binding (FIG. 3). PF-06651600 is being tested for the treatment of rheumatoid arthritis and alopecia areata, and a trial is planned for ulcerative colitis[181] (NCT02969044, NCT02974868 and NCT02958865).

TYK2-selective inhibitors. TYK2-selective inhibitors have been developed[182,183] with the goal of blocking signalling downstream of the cytokines IL-6, IL-12 and IL-23, all of which are implicated in the pathogenesis of various autoimmune diseases[1]. Investigational TYK2 inhibitors have shown exciting preclinical efficacy in models of psoriasis, lupus and inflammatory bowel disease[182,184]. BMS986165 is a TYK2 inhibitor that was discovered by using a phenotypic screen of kinase inhibitors to identify ligands of the TYK2 pseudokinase domain. The pseudokinase domain was then targeted on the basis of crystallographic structural information, resulting in allosteric inhibition[184,185]. BMS986165 ameliorates disease in preclinical models of SLE and IBD, and a phase II trial is currently ongoing for the treatment of psoriasis[184] (NCT02931838). Other TYK2 inhibitors, such as NDI-031232 and NDI-031407, were developed by using structure-based design and are being tested in preclinical models[182,183]. Finally, several new inhibitors in phase I trials inhibit both JAK1 and TYK2. PF-06700841 was developed using a structurally enabled programme in combination with high-throughput screening and is being tested in psoriasis and alopecia areata, with plans for a trial in IBD[186] (NCT02969018, NCT02974868 and NCT02958865). SAR-20347 was discovered with high-throughput computational screening followed by secondary screening against a panel of 291 kinases and is effective in mouse models of inflammatory skin disease[187]. Given the differences between the *in vitro* and *in vivo* selectivity of other jakinibs, this and other trials will determine whether TYK2-blockers are selective in clinical practice and how selectivity might affect outcomes.

JAK inhibitors that also inhibit other kinases. Several JAK inhibitors that have been tested for immune-mediated disease also inhibit non-JAK kinases, most notably spleen tyrosine kinase (SYK). SYK is a critical kinase used by a number of multichain immune recognition receptors[188]. In principle, targeting SYK along with JAKs could enhance efficacy by broadening the

signalling pathways that are blocked; however, this broad inhibition could also be associated with severe adverse events. The SYK inhibitor fostamatinib was effective in the treatment of rheumatoid arthritis but was associated with hypertension[189]. Fostamatinib is currently being evaluated for the immune-mediated diseases autoimmune haemolytic anaemia, immune-mediated thrombocytopenic purpura and immunoglobulin A nephropathy (NCT 02076412, NCT02612558, NCT02077192 and NCT02112838)[189]. The topical dual JAK and SYK inhibitor R348 did not meet the end points of improved tear production and corneal fluorescein staining, a marker of damage, for the treatment of dry eye disease (NCT01900249). R348 was mildly efficacious at reducing corneal fluorescein staining in ocular GVHD[190].

The active metabolite of R348, R333, a topical drug that was tested for the treatment of discoid lupus erythematosus, also failed to meet its primary end point (NCT01597050). Another JAK and SYK inhibitor, cerdulatinib, was discovered using extensive structure–activity relationship studies and has demonstrated efficacy in an animal arthritis model[191].

SB-1578 is a multikinase inhibitor, acting on JAK2, CSF1 receptor (CSF1R; also known as the M-CSF receptor) and receptor-type tyrosine-protein kinase FLT3. CSF1R and FLT3 are receptor tyrosine kinases that promote myelopoiesis and haematopoiesis, respectively[192,193]. Mutations in FLT3 and CSF1R cause haematopoietic malignancy, and both kinases are also implicated in the pathogenesis of rheumatoid arthritis. As in the case of the combination JAK–SYK inhibitors discussed above, simultaneous blockade of three discrete signalling pathways with agents such as SB-1578 might increase efficacy but could also exacerbate adverse effects[194]. SB-1578 was developed by modifying the structure of pacritinib, a multikinase inhibitor under investigation for myelofibrosis and various malignancies, to achieve an improved therapeutic window[195]. SB-1578 was effective in the preclinical model of collagen-induced arthritis[194]. A phase I trial in healthy subjects was completed in 2012, but results were not made available and further development has not taken place (NCT01235871).

Box 1 | **Lesson learned from jakinibs**

When development of Janus kinase (JAK) inhibitors first began, certain characteristics of these agents were predicted based on scientific understanding of the roles various JAKs played in biological processes. Use of these medications in large-scale clinical trials has validated some of these predictions but has also produced a number of unpredictable findings. Certain key questions in the field remain unanswered, and data emerging from new trials will help to resolve these uncertainties.

Predicted

- Target broad spectrum of cytokines
- Efficacious for autoimmune adaptive immunity-mediated disease
- Adverse effects such as infection, anaemia and cytopenia

Not predicted

- Useful and efficacious for autoinflammatory innate immunity-mediated disease
- Hyperlipidaemia as an adverse effect
- Selectivity is unnecessary
- Pan-jakinibs are viable
- JAK2 inhibitors are viable
- JAK1 inhibitors are viable

Unknown

- Is selectivity achievable?
- Is selectivity advantageous?

Future directions

The past decade has witnessed an explosion of data regarding the efficacy of selective and non-selective jakinibs in the treatment of autoimmune diseases. In many respects, the success of jakinibs was predictable on the basis of genetic models. What was less predictable was their relative safety (BOX 1). Jakinibs therefore serve as an interesting model for other drugs designed to target key intracellular signalling pathways.

Still, critical questions with immediate clinical relevance remain unanswered, providing several areas of research for future investigators. Among the most exciting of these is the possibility that tofacitinib may be efficacious against debilitating, treatment-refractory autoimmune diseases. Immune-mediated diseases such as SLE, IBD and dermatomyositis have fewer treatment choices than rheumatoid arthritis or psoriasis. With multiple early-phase clinical trials in such diseases underway, the next few years should begin to establish the efficacy and safety of various JAK inhibitors in such diseases (NCT03159936, NCT02535689, NCT02708095, NCT03002649 and NCT03026504).

Next, the benefits, risks and optimal mechanisms for achieving *in vivo* selectivity remain elusive. Although many next-generation jakinibs are reasonably selective *in vitro,* their selectivity in the clinical arena is not as fully characterized and remains to be proved. Moreover, current studies indicate that selective and pan-jakinibs are equally effective for rheumatoid arthritis, but the same may not be true for other immune-mediated diseases. For example, the JAK1-selective filgotinib ameliorates Crohn's disease considerably, whereas tofacitinib does not. This difference raises the question of which cytokines are being differentially inhibited by filgotinib and tofacitinib and how various JAK isoforms contribute to Crohn's disease pathophysiology. It also raises the prospect that selective blockade of one JAK isoform over another may be sufficient or even advantageous in certain immune-mediated diseases[196], although blockade of multiple JAKs may be necessary in other settings[197]. Moreover, other kinase inhibitors such as sunitinib and dasatinib have activity against JAKs[198], raising the prospect that wider blockade of multiple signalling pathways may provide additional therapeutic benefit for refractory immune-mediated diseases, although the risks must be carefully balanced. As the spectrum of jakinib-responsive disease expands, perhaps even including IL-13-driven fibrotic diseases such as beryllosis[199], the risks and benefits of JAK isoform selectivity in different rheumatic diseases will become increasingly clear and may contribute to our understanding of disease pathogenesis.

For jakinib-responsive diseases, it is still unknown which patients would derive the most benefit from JAK blockade; the current ACR guidelines recommend tofacitinib for the treatment of cDMARD-refractory established rheumatoid arthritis but do not distinguish between tofacitinib and bDMARDs. Clearly, the field needs more rational treatment selection: in clinical trials, 30–40% of patients with rheumatoid arthritis invariably fail to respond to therapy. Although most patients with rheumatoid arthritis can be successfully treated with FDA-approved agents, we are currently unable to predict which therapy will be most effective for any particular patient. This uncertainty may be because most polygenic autoimmune diseases are heterogeneous[1], such that JAK-dependent cytokines might drive disease in a large subset of patients, and other cytokines could be more important for different subgroups. A vigorous search is currently under way to identify biomarkers that could predict response to various immunomodulatory agents, including jakinibs. With improved success in treating diseases like rheumatoid arthritis, the prospect emerges of cure or long-term remission. Many believe that those goals will require more aggressive, early treatment of patients. One might expect that trials using jakinibs in early rheumatoid arthritis will be considered. In addition, one can imagine tapering patients off MTX when their disease comes under control; this, too, should be investigated in clinical trials.

Another area that remains to be established is the optimal dosing regimen for jakinibs. Currently, all clinical trials use an identical dose for induction of remission and for maintenance therapy. However, preclinical data suggest that chronically treated cells become less responsive to JAK-dependent cytokines, or permanently inhibited, even after a washout period[200], when they are not being treated with jakinibs. This finding raises the possibility that jakinibs could be dosed aggressively to induce remission, then tapered to a much lower dose for maintenance therapy[200]. This regimen is already the standard practice in canines, in which oclacitinib is administered b.i.d. for up to 14 days and once daily thereafter as maintenance therapy.

Some patients with a spectrum of systemic autoimmune diseases develop limited cutaneous, mucosal or ocular autoimmunity. The possibility of successfully treating such manifestations with topical formulations could be associated with fewer adverse effects. Topical formulations of tofacitinib and ruxolitinib have been investigated in the preliminary studies reviewed above; however, these studies are still in their infancy.

Similarly, the relative risks and benefits of jakinibs as monotherapy and as combination therapy with other immunomodulators such as MTX or even biologics[201] remain incompletely characterized. As the renal transplant studies have shown, this strategy is not without risk, but it could potentially be managed by using a serum concentration-based dose escalation protocol or immunological functional studies to gauge early response to therapy. As with corticosteroids, there might be a role for bDMARDs with long half-lives as maintenance therapy, whereas potent targeted synthetic DMARDs with short half-lives could be used for breakthrough activity. This strategy could be particularly relevant to catastrophic flares of systemic autoimmune diseases, in which current standard of care aims to immunosuppress patients profoundly and induce remission, then follow up with less toxic consolidation and maintenance therapy.

Along these lines, our understanding of immunopathology is becoming increasingly refined as we begin to incorporate recent discoveries about the role of non-coding, regulatory DNA elements[202]. Such elements may be relatively close to genes but can also be far away. Moreover, some key genes are surrounded by dense regions of regulatory elements termed 'superenhancers'. In T cells, genes with superenhancer structure seem preferentially affected by jakinibs[202]. As our understanding of the immense numbers of regulatory elements becomes clearer, physicians may be able to fine-tune the expression of critical disease regulators, rather than simply turning them on or off. In this way, the effect of immunomodulation might be optimized and adverse effects minimized.

Finally, a host of novel jakinibs are being developed (TABLE 4), with at least 95 patented candidates[160,161]. Many are analogues of FDA-approved compounds, but some have achieved unprecedented selectivity by covalently targeting non-conserved residues at the kinase domain. As the field evolves, jakinibs thus continue demonstrating clinical efficacy as immunomodulators while also providing critical insights into the mechanisms driving immune-mediated disease.

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Competing interests statement
J.O'S. declares that he and the US Government receive royalties based on patents related to the targeting of Janus kinases. J.O'S., M.G. and the US Government have had longstanding Cooperative Research and Development Agreements with Pfizer, which produces tofacitinib, a Janus kinase inhibitor.