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JAK-inhibitors. New players in the field of immune-mediated diseases, beyond rheumatoid arthritis

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Abstract

Janus kinase (JAK)/signal transducers and activators of transcription (STATs) are a group of molecules associated with one of the major pathways through which many cytokines exert and integrate their function, and as such they are increasingly recognized as playing critical role in the pathogenesis subserving various immune-mediated diseases, including RA, PsA, SpAs, IBD, skin disorders (e.g. alopecia areata, atopic dermatitis), single-gene disorders like interferonopathies, and others. JAKs are the key initiating players of the JAK/STAT pathway. Upon binding of their respective effector molecules (cytokines, IFNs, growth factors and others) to type I and type II receptors, JAKs are activated, and through phosphorylation of themselves and of other molecules (including STATs), they mediate signal transduction to the nucleus. A class of drugs—called JAK inhibitors or JAKinibs—that block one or more JAKs has been developed in the last decade, and now numbers >20 members. Although, so far, JAK inhibitors have been marketed only for RA and PsA, these drugs have been tested in phase 2 and phase 3 clinical trials for other inflammatory conditions and beyond. In this review, we summarize the clinical data, including efficacy and safety, available for JAK inhibitors used in some immune-mediated conditions other than RA.

Key words: JAK/STAT pathway, JAK inhibitors, immune-mediated diseases

Rheumatology key messages

- Janus kinase inhibitors are increasingly being tested for inflammatory diseases other than RA.
- The value of different Janus kinase inhibitors' specificities across disease states remains to be defined.
- The acceptable safety profile of Janus kinase inhibitors, across disease states, remains to be confirmed.

Introduction

In recent years, advances in the field of basic and translational research have identified pathways and molecular targets at the subcellular level that regulate immune responses, leading in turn to the development of many new drugs.

One of these is the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway, which appears to have a pivotal role in the pathogenesis of many immune-mediated diseases, by facilitating the signal transduction of many different cytokines and other molecules [1]. During the last decade, drugs known as JAK inhibitors or JAKinibs, blocking one or more of the molecules involved in this pathway, have been developed and tested in clinical trials for many different indications. Although the focus of JAK inhibitors for the treatment of chronic inflammatory conditions has been on RA, there are other conditions in which JAKinibs could serve as therapeutic options [2]. Herein, we describe the immune-mediated rheumatological indications—other than RA—for which JAK inhibitors have been approved or tested in clinical trials. We also present the basic principles of their mode of action and the consequent safety concerns raised.

The JAK/STAT pathway

JAKs, named after the two-faced Roman God *Janus*, form a family consisting of four members: JAK1, JAK2, JAK3 and TYK2. They are all cytoplasmic tyrosine kinases able to phosphorylate tyrosine residues either on themselves

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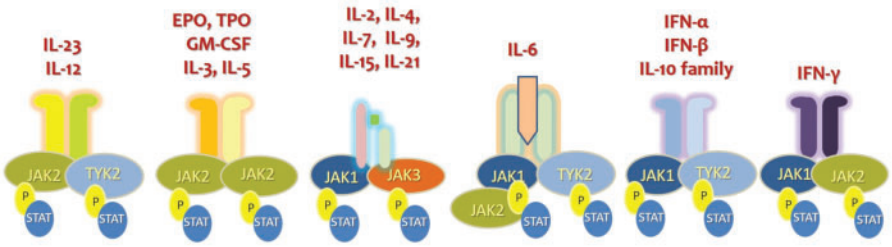
Fig. 1 Schematic representation of the various cytokines and their receptors signalling via the JAK/STAT signal-transduction pathway



EPO: erythropoietin; TPO: thrombopoietin; JAK: Janus kinase; TYK: tyrosine kinase; P: phosphorus; STAT: signal transducer and activation of transcription.

(autophosphorylation) or on adjacent molecules (trans-phosphorylation), including the STATs. The latter is a family of transcription factors, acting downstream of JAKs and consisting of 7 members [3]. The JAK/STAT pathway is an evolutionarily conserved pathway mediating the effect of many different molecules, including ILs, IFNs, colony-stimulating factors, growth factors and hormones (also known as hormone-like cytokines), which exert their function through type I and type II receptors [3] (Fig. 1). Type I receptors are used by several ILs, colony-stimulating factors and hormones, while type II receptors are used by IFNs and IL-10–related cytokines (IL-10, IL-19, IL-20, IL-22, IL-22 and IL-26) [3]. These receptors consist of various subunits, each of them associated with a JAK molecule. Upon ligation of the effector protein with its receptor, the latter is oligomerized, leading to activation of the relevant JAK, which, in turn, is autophosphorylated and also transfers a phosphate to a tyrosine residue in the receptor's subunit, creating a docking site for a STAT molecule. The STAT molecule is also phopsphorylated by the JAK. Subsequently, STATs are dimerized and translocate from cytosol to the nucleus, thereby regulating gene expression [2].

Receptor subunits are associated with a specific JAK; some of them may be associated with more than one JAK. Also, as the JAK family has only four members, many different cytokines may act through the same JAK. Consequently, inhibiting a JAK molecule may impede more than one pathway, which may in part explain both the efficacy obtained and some of the adverse effects observed with JAK inhibitor treatment [4].

Many JAKinibs have been developed over recent years (Table 1), often subcategorized as first-generation and newer JAKinibs. The first-generation JAKinibs do not display high specificity, demonstrating activity against three or even all four of the JAK family members (also termed as pan-JAK inhibitors). Selectivity against specific JAKs is a desirable feature of the newer JAKinibs, primarily in terms of mitigating side effects. Currently only two JAKinibs have approval for the treatment of RA and PsA. However, these and other JAK inhibitors appear to also have a potential position in the treatment of many other autoimmune diseases, including: SpAs; psoriasis and other skin diseases such as atopic dermatitis (AD) and alopecia areata (AA); IBD; uveitis; GCA; and single-gene disorders, such as the so-called interferonopathies.

PsA and SpAs

The potential mode of action of JAKinibs in psoriatic disease is not fully understood. However, there are data from animal models and *ex vivo* experiments suggesting that the JAK/STAT pathway is linked to the IL-23/-17 axis, which in turn plays a crucial role in the underlying pathogenesis of PsA and spondyloarthropathies. Although IL-17 *per se* does not seem to employ the JAK/STAT pathway [5], IL-23 (which is an upstream driver of IL-17A release) exerts it's function through the JAK2-TYK2/STAT3-STAT4 system [4, 6, 7]. Additionally, IL-22 (also a key player in the pathogenesis of SpAs and an important mediator of the IL-23/-17 axis) uses the JAK/STAT pathway [4, 6]. Finally, type I IFNs are also implicated in some elements of the PsA articular and cutaneous response.

In animal arthritis models, JAKinibs have been found to inhibit, dependent on the cytokine environment, the expression of Th17-related cytokines (IL-17A, IL-17F, IL-22), thereby blocking the IL-23/-17 axis [8]. *Ex vivo* studies have shown that in synovial fluid samples obtained from patients with PsA, proteins involved in (or functionally related to) the JAK/STAT pathway [JAK1, Extracellular signal-Regulated Kinase (ERK) 1/2, STAT1, STAT3, STAT5] are increased [9]. The coculture of synovial fibroblasts derived from PsA patients or PsA synovial explants with tofacitinib (a first-generation JAK3/1 inhibitor with less activity for JAK2 and possibly TYK2) led to reduced expression of phosphoproteins involved in the pathway, decreased ability of fibroblasts to form networks and migrate, and decreased secretion of inflammatory cytokines and effector proteins, such as metalloproteinases [10]. Additionally, a recently published study demonstrated that tofacitinib inhibited phosphorylation of JAK2 and STAT3 induced by IL-23 in peripheral blood mononuclear cells from PsA patients, and hindered proliferation of $CD4^+CD11^+CD45RO^+IL\text{-}17^+$ T cells (also known as $IL\text{-}17^+$ effector memory cells) in peripheral blood mononuclear cells and mononuclear synovial fluid cells from PsA patients [7, 11]. These findings suggest a link between

Table 1 JAK inhibitors tested in clinical trials for the management of immune-mediated diseases

Name	JAK specificity	RA	PsA and SpA	Psoriasis	IBD	Interferonopathies	Skin diseases	Other
Tofacitinib	JAK3/JAK1 > JAK2, TYK2	Approved	Approved (PsA) Phase 2 (AS)	Phase 3	Phase 3 (UC)		Phase 2 (AA) Phase 2 (AD)	Phase 1 (SLE, DLE) Phase 1 (DM) Phase 1 (dSc)
Ruxolitinib (INCB18424)	JAK1/JAK2 > TYK2	Phase 2		Phase 2	Phase 2 (CD)	Case reports/ case series	Phase 2 (AA) Phase 2 (AD) Phase 2 (Vit)	Phase 2 (HPS)
Baricitinib (INCB28050)	JAK1/JAK2	Approved		Phase 2		Compassionate programme	Phase 3 (AD)	Phase 2 (GCA) Phase 2 (SLE)
Peficitinib	Pan-JAK (some selectivity for JAK3)	Phase 3		Phase 2	Phase 2 (UC)			
Decernotinib[a]	JAK3	Phase 2/3						
Filgotinib	JAK1	Phase 3	Phase 2 (PsA) Phase 2 (AS)		Phase 3 (CD) Phase 3 (UC)			Phase 2 (SS) Phase 2 (NIU) Phase 2 (CLE) Phase 2 (LN)
Solcitinib[b]	JAK1			Phase 2	Phase 1 (UC)			Phase 2 (SLE)
Itacitinib (INCB039110)	JAK1	Phase 2		Phase 2				
SHR0302	JAK1 > JAK2, JAK3	Phase 2						
Upadacitinib	JAK1	Phase 3	Phase 3 (PsA) Phase 2 (AS)		Phase 3 (CD) Phase 3 (UC)			
PF-04965842	JAK1			Phase 2			Phase 3 (AD)	

[a]Development on hold. [b]Terminated due to safety issues. JAK: Janus kinase; UC: ulcerative colitis; AA: alopecia areata; AD: atopic dermatitis; dSc: diffuse scleroderma; CD: Crohn's disease; Vit: vitiligo; HPS: hemophagocytic syndrome; NIU: non-infectious uveitis; CLE: cutaneous lupus erythematosus.

JAKinibs and the IL-23/-17 axis and therefore partially explain the effectiveness of this drug class in PsA and SpAs.

A recent clinical research programme led to the Food and Drug Administration approving tofacitinib for PsA. The results from large phase 3 trials have recently been published. In summary, a placebo and adalimumab controlled, 12-month, double-blind study demonstrated that tofacitinib in doses of 5 mg bd (twice a day) or 10 mg bd was superior to placebo in active PsA patients who were non-responders to conventional DMARDs. Significantly more patients treated with tofacitinib achieved the primary end points [ACR20 and changes in HAQ score] at week 12, compared with placebo; (ACR20 response rates; tofacitinib 5 mg: 50%; tofacitinib 10 mg: 61%; versus placebo: 33%, $P = 0.01$ and $P < 0.001$, respectively). Significant differences in the ACR20 rates were already observed from week 2. Most of the secondary end points (including at least 75% improvement in Psoriasis Area and Severity Index (PASI75) score, ACR50 and ACR70) were also achieved, at week 12, in significantly higher rates in both groups treated with tofacitinib versus placebo. A significantly greater decrease in the Leeds enthesitis index was observed for the 10 mg-treated, but not for the 5 mg-treated group versus placebo. The results were maintained until month 12. Although not designed specifically for this purpose, both tofacitinib-treated groups showed similar efficacy to the adalimumab group. Finally, at month 12, >90% of the patients across all groups met the criteria for radiographic non-progression in the joints. [12] In a linked study reported in the same journal, PsA patients with inadequate response to biologic drugs were randomized to receive tofacitinib 5 mg bd or 10 mg bd, or placebo [13]. At week 12, patients who received the active drug achieved the primary end point (ACR20 and changes in HAQ scores) in statistically significantly higher percentages (ACR20 response rates tofacitinib 5 mg: 50%; tofacitinib 10 mg: 47%) and most of the secondary end points (ACR50, PASI75—the difference in PASI75 was not statistically significant for tofacitinib 5 mg bd) compared with those who received placebo (ACR20: 24%). The results were maintained until month 6 [13]. Phase 2 and phase 3 clinical trials are underway to assess the efficacy and safety of other, next generation JAKinibs like the JAK1 inhibitors filgotinib (ClinicalTrials.gov— NCT03101670, NCT03320876) and upadacitinib (ClinicalTrials.gov—NCT03104374, NCT03104400) in PsA.

The promising results of JAKinibs in the field of inflammatory arthritis and the fact that polymorphisms in JAK2 and STAT3 have been associated with susceptibility to AS [14, 15] paved the way for the investigation of these reagents as treatments for AS. Favourable results have recently been published from a phase 2, placebo-controlled, dose-ranging study, in which AS patients were randomized to one of three doses (2 mg, 5 mg, 10 mg; all bd) of tofacitinib [16]. Patients on 5 mg bd achieved the primary end point [ASAS20 (Assessment in AS 20% improvement)] at week 12, at significantly higher rates compared with placebo (tofacitinib 5 mg: 80.8%; placebo: 41.2%, $P < 0.001$). At the same time point, patients at all doses of tofacitinib achieved most of the secondary end points, including ASAS40 (ASAS 40% improvement), BASDAI50 (BASDAI 50% improvement), improvement at Spondyloarthritis Research Consortium of Canada (SPARCC) spine scores and quality of life indices. Furthermore, the 5 mg bd and 10 mg bd groups demonstrated significant differences at week 12, compared with placebo, in SI joint SPARCC scores and in enthesitis, as assessed by the change from baseline in the Maastricht AS Enthesitis Score index. In a *post hoc* analysis of this study, with a focus on the magnetic resonance imaging findings in these patients [17], it was shown that Minimally Important Changes for SPARCC spine and SPARCC SI joints scores were achieved in approximately one-third of the patients treated with tofacitinib. A greater proportion of patients who achieved Minimally Important Changes, compared with those who did not, achieved clinically meaningful responses, like ASAS20 and ASAS40. Phase 2 studies are underway evaluating the efficacy and safety of filgotinib and upadacitinib in AS (NCT03117270, NCT03178487, respectively).

Psoriasis

Psoriasis is another condition for which JAK inhibitors appear to be a very promising therapeutic option. In essence, the rationale for their use maps to that laid out for PsA and AS. Thus, many of the molecules with an active role in the pathogenesis of psoriasis, like IL-23, IL-22, IL-15 and IFNγ [18–20], employ the JAK/STAT pathway to mediate their function.

Phase 2 trials, assessing the safety and efficacy of tofacitinib in patients with psoriasis, carried out after promising results from phase 1 studies [21], showed clinical improvement in psoriasis, as assessed by the PASI75 response at week 12 [22, 23]. Quality of life indices were also improved by tofacitinib [22].

Phase 3 trials confirmed these early phase results. In two large studies (OPT Pivotal 1 and OPT Pivotal 2), with similar protocols, it was demonstrated that psoriasis patients who received tofacitinib (5 mg or 10 mg, both bd), achieved PASI75 at week 16 in higher percentages (OPT Pivotal 1, 5 mg: 39.9%; 10 mg: 59.2% and OPT Pivotal 2, 5 mg: 46.0%; 10 mg: 59.6%), compared with those received placebo (OPT Pivotal 1: 6.2%; OPT Pivotal 2: 11.4%) [24]. The results were maintained until month 24 [25]. Improvement in nail psoriasis, as assessed by the Nail Psoriasis Severity Index score, was also observed at week 16 and generally maintained until week 52 [26]. Additionally, a separate phase 3, 12-week trial, examined the noninferiority of tofacitinib versus etanercept, having as co-primary end points the proportion of patients achieving PASI75 and Physician Global Assessment scores of 'clear' or 'almost clear'. Patients with stable psoriasis were randomized to receive tofacitinib 5 mg bd, tofacitinib 10 mg bd, etanercept 50 mg twice weekly, or placebo. The results showed that tofacitinib 10 mg bd, but not 5 mg bd, was superior to placebo and not inferior to etanercept at week 12, as assessed by the percentage

of patients achieving the PASI75 response (5 mg: 39.5%; 10 mg: 63.6%, etanercept: 58.8; placebo: 5.6%) and the Physician Global Assessment scores [27]. In a linked study [28], patient-reported outcomes were significantly improved for tofacitinib- and etanercept-treated patients versus placebo. In summary, by week 12, all active groups achieved a Dermatology Life Quality Index score of 0 or 1 in significantly higher percentages compared with placebo ($P < 0.0001$, for all comparisons). Also, the proportion of patients with a patient's global assessment for psoriasis score of 0 or 1, from week 4 and onwards, was significantly higher for all active-treatment groups, compared with placebo ($P < 0.0001$, for all comparisons). Finally, itchiness [measured by Itch Severity Item] was also significantly improved, already from day 1 in both tofacitinib-treated groups versus placebo ($P < 0.05$, for both). The 10 mg-tofacitinib-treated group achieved an Itch Severity Item score of 0 or 1 in a greater percentage of patients compared with etanercept, from week 2 up to week 12 ($P < 0.05$ for all comparisons). Another phase 3 trial showed that treatment withdrawal of tofacitinib led to flare of psoriasis in more than half of the cases. Retreatment recovered efficacy in ~60% of the patients. The reason for that is currently unknown. Development of anti-drug antibodies has been suggested to explain similar phenomena occurring in patients treated with monoclonal antibodies. However, this mechanism does not apply for treatment with tofacitinib, given that it is a small molecule and thus non-immunogenic [29]. Topical application of tofacitinib ointment (2%) for psoriasis has also been tested in a phase 2 trial and was found superior to placebo at week 8, but not at week 12 [30].

Baricitinib (a JAK1/2 inhibitor) was tested in a phase 2 trial in psoriasis. Patients who received 8 mg or 10 mg per day achieved significantly higher PASI75 response rates at week 12, compared with placebo [31]. The majority of the responders maintained their scores through week 24 [31]. In another phase 2 trial, peficitinib (a pan-JAK inhibitor with moderate selectivity for JAK3 over the other JAKs), orally administrated, demonstrated dose-dependent clinical and histological improvement *versus* placebo at week 6 [32]. Treatment with the selective JAK1 inhibitors PF-04965842 and Solcitinib (GSK2586184) in phase 2 trials, was also found to be more effective than placebo at weeks 4 and 12, respectively [33, 34].

Topical application of ruxolitinib (a JAK1/2 inhibitor approved for the treatment of myeloproliferative diseases) in patients with psoriasis, resulted in clinical improvement and downregulation of transcriptional markers of immune activation in lesional skin [35]. Decreased dermal inflammation and epidermal hyperplasia was also observed [35, 36]. Phase 2 trials are ongoing for topical ruxolitinib treatment in patients with plaque psoriasis (NCT00617994, NCT007787700).

Phase 2 trials are also underway evaluating the safety and efficacy of various other JAKinibs (like INCB039110-itacitinib) in patients with plaque psoriasis (NCT01634087).

Other skin diseases

Apart from psoriasis, JAK inhibitors also seem to be effective for some other skin diseases; often their pathogenesis implicates IFN and ILs acting through type-I cytokine receptors as important mediators. In AA animal models, it was shown that IL-2, IL-15 and IFN-γ play a significant role in the pathogenesis [37]. Given that they all act through the JAK/STAT pathway, it was reasonable to hypothesize that JAK inhibitors would be promising therapeutic agents. Indeed, initial small studies indicated that treatment with ruxolitinib led to decreased perifollicular infiltration of T cells, normalization of inflammatory signatures and clinical improvement with hair regrowth after 3–5 months of systemic treatment [38]. Two small, open label-studies assessing the efficacy of tofacitinib were recently published. The first one demonstrated that in patients with AA and its variants, alopecia totalis and alopecia universalis, 3-month treatment with tofacitinib led to significant improvement in approximately two-thirds of the patients [39]. However, the disease flared-up when treatment was discontinued. A smaller, open-label, study and a retrospective study also reported that tofacitinib was efficacious for the treatment of AA and its variants [40, 41]. Of note, tofacitinib appears to also be helpful for the treatment of nail dystrophy in the context of AA [42]. Topical treatment with tofacitinib had less impressive results compared with oral administration, helping approximately 30% of the patients in a small, open-label study [43]. These results have also been replicated in an adolescent population [44]. A phase 2 clinical trial of topical tofacitinib for AA is ongoing (NCT02812342). Promising results were also obtained from a pilot, open-label study, in which patients with moderate to severe AA were treated with oral ruxolitinib. At month 6, the vast majority of the patients (75%) displayed significant improvement [45]. Topical treatment with ruxolitinib has also been reported in case reports with conflicting results [46, 47]. A phase 2 trial was recently completed, but no results have been published yet (NCT02553330).

AD is another skin disease for which JAKinibs could serve as an attractive treatment modality. Th2 cells are thought to be the hierarchical driving cells in the pathogenesis of AD, interacting with altered skin barrier function. IL-4, acting through its receptor, which is associated with JAK1/JAK3, is the main cytokine implicated in AD, through promoting and inhibiting differentiation of Th2 cells and keratinocytes, respectively [48, 49]. Tofacitinib has been tried as a systemic treatment for AD in a small study with good results [50], while a phase 2, placebo-controlled study has also been published, indicating that AD patients treated with topical applications of tofacitinib experienced significant improvement at week 4, with favourable results being evident from week 1 [51]. A recently published study, reported that baricitinib was better than placebo at week 16 for AD treatment [52]. In addition, there are ongoing phase 2 and phase 3 trials assessing the safety and efficacy of topical ruxolitinib (NCT 03011892) and systemic administration of PF-04965842 (NCT03349060,

NCT03422822), baricitinib (NCT 03428100, NCT 03435081, NCT 03334435, NCT03334422, NCT 03334396) and upadacitinib (NCT 02925117) in AD.

JAKinibs have also been examined as potential treatment for vitiligo, given the central role of IFN-γ in its pathogenesis [53]. Both tofacitinib and ruxolitinib have been tested with good results, although the disease relapses after treatment discontinuation [54, 55]. A small proof-of-concept study for topical ruxolitinib yielded promising results, especially for facial vitiligo [56]. Another phase 2 clinical trial of local treatment with ruxolitinib is currently underway (NCT02809976).

IBD

Genome-wide association and other studies have shown association between genetic variants in JAK2, STAT3, TYK2 genes, and IL-23 receptor gene and Crohn's disease (CD) [57–59]. Also, various cytokines, including IL-12, IL-23, IL-21, IL-22, IL-27 and IFN-γ, have been identified as playing a key role in the pathogenesis of CD. These molecules exert their action via the JAK–STAT pathway, involving all members of the JAK family, making thus, JAKininbs an attractive treatment option for CD [6, 57, 60]. However, results for tofacitinib in CD were not encouraging, as no difference was seen in clinical response or clinical remission for various doses, versus placebo [61, 62]. In contrast, filgotinib and upadacitinib reported favourable results in phase 2 studies, perhaps reflecting the close regulatory inflammatory cross talk in leucocyte subsets (e.g. Treg *vs* Tresponder) within the gastrointestinal mucosa and their differential sensitivity to discrete JAK pathway inhibition, especially of JAK1, while sparing JAK3. In summary, patients with moderate to severe CD were randomized to treatment with filgotinib or placebo [63]. At week 10, significantly more patients in the active-drug arm compared with placebo achieved clinical remission [Crohn's disease activity index (CDAI) < 150] and clinical response (drop of CDAI of >100) [63]. Phase 3 trials are ongoing to evaluate filgotinib as induction or maintenance treatment in CD (NCT02914561, NCT02914600). In another study, patients with moderate to severe CD refractory to treatment with TNF inhibitors were treated with various doses of upadacitinib or placebo. At week 16, compared with placebo, significantly more patients on 6 mg upadacitinib twice a day, achieved clinical remission, and all patients receiving doses $\geqslant$6 mg achieved endoscopic response [64]. Several phase 2 and phase 3 studies are ongoing to evaluate the efficacy and safety of the drug as induction therapy in patients with CD resistant to conventional or biologic treatments, and also to assess its feasibility as maintenance treatment for CD (NCT03345836, NCT03345849, NCT03345823, NCT02365649, NCT02782663).

As regards ulcerative colitis (UC), tofacitinib appears to be a promising therapeutic [61]. In a phase 2, placebo-controlled trial, patients with moderate to severe UC were randomized to receive various doses of tofacitinib. Patients who received 15 mg bd achieved clinical response at week 8 at a significantly higher rate compared with placebo. Clinical remission (defined as a Mayo score $\leqslant$2 with no subscore >1) was also achieved at week 8 by patients receiving 3 mg bd or higher doses of tofacitinib [65]. Subsequently, three phase 3 trials (OCTAVE programme) reported that more patients with moderate to severe UC who had failed conventional or biologic therapy but were treated with 10 mg bd of tofacitinib achieved higher rates of clinical remission, clinical response and mucosal healing at week 8, compared with placebo [66]. In addition, it was shown that remission occurred more frequently at week 54 in patients who received tofacitinib 5 mg or 10 mg bd as a maintenance treatment for UC, compared with placebo [66]. Furthermore, quality of life indices were significantly improved in patients treated with tofacitinib, evident from week 8, and the difference was maintained until week 54 [67].

A phase 2 trial evaluating peficitinib (also known as JNJ-54781532) has been completed, but the results are not yet available (NCT01959282), and phase 3 trials assessing the safety and efficacy of upadacitinib (NCT03006068, NCT02819635) and filgotinib (NCT02914535, NCT02914522) as induction or maintenance treatment for UC are currently underway.

Single-gene disorders (interferonopathies)

Type I interferonopathies are a heterogeneous group of autoinflammatory disorders incorporating phenotypically different diseases like Aicardi–Goutières syndrome, chilblain lupus, Stimulator of interferon genes–Associated Vasculopathy with onset in Infancy (SAVI), Singleton–Merten syndrome, retinal vasculopathy with cerebral leukodystrophy, Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE) and others [68]. In these disorders, genes involved in the IFN-I signalling pathway are aberrantly expressed, leading to its upregulation. In the canonical IFN-I pathway, IFN-I binds to the IFN-I receptor—constituted by two chains: IFN-I receptor 1 and IFN-I receptor 2—which activates JAK1 and TYK2. Subsequently, STAT1 and STAT2 are phosphorylated and activate IFN Type-I–stimulated genes [69]. Therefore, it has been suggested that JAK inhibition could be a reasonable approach in the treatment of these disorders.

There are some initial promising results. SAVI is a recently described interferonopathy associated with gain-of-function mutations in *TMEM173* encoding stimulator for interferon genes [70]. Ruxolitinib appears to be a therapeutic option for these patients. In a case-series report, three SAVI patients treated with ruxolitinib exhibited significant symptomatic improvement, accompanied by a decrease in IFN-stimulated genes in two patients [71]. Similarly, two patients from a family with chilblain lupus associated with mutated stimulator of interferon genes treated with tofacitinib 5 mg bd displayed clinical improvement, along with suppression of the IFN signature [72], while a another case study reported a patient with the same disease successfully treated with ruxolitinib [73]. Ruxolitinib has also been used in patients with Aicardi–Goutières syndrome with good response [74]. Also, in 2011, the Food and Drug Administration–approved compassionate programme (NCT01724580) was initiated. In this program, patients

with CANDLE or SAVI were included, to receive treatment with baricitinib [75]. The optimal dosing of JAKinibs in interferonopathies is still to be resolved, as the pharmacodynamics may be affected by renal function and weight [75].

Eye diseases

In an experimental autoimmune uveitis model, topical treatment with tofacitinib (0.03%) three times a day was found to improve uveitis, clinically and histologically, and to reduce the intravitreous levels of inflammatory cytokines and their gene expression in both the iris–ciliary body and the retina/choroid [76, 77]. A phase 2 clinical trial is underway assessing the efficacy and safety of orally administrated filgotinib in patients with non-infectious uveitis (NCT03207815).

GCA

Recent studies support the notion that JAK inhibitors could be potentially efficacious in patients with GCA. In a chimeric model, where vascular inflammation was induced in human vessels engrafted to immunodeficient mice, treatment with tofacitinib reduced proliferation rates of lesional T cells and the production of IFN-γ, IL-17 and IL-21 [78]. Micro-angiogenesis, outgrowth of the intima and the number of the CD4+CD103+ T memory cells were also reduced [78]. A phase 2 study, testing the safety and efficacy of baricitinib in relapsing GCA, is underway (NCT03026504).

Safety of JAKinibs

To date, the safety profile of JAKinibs appears to be acceptable and comparable with those of biologic drugs used for the treatment of immune-mediated diseases. Most of the safety data come from the large trials of tofacitinib in RA, while evidence for other JAKinibs continues to accumulate. At this time, therefore, much of the safety inference must come from the large RA cohorts—it is not yet clear whether other diseases will bring with them novel adverse event profiles. As summarized in a recently published analysis using data from phase 1–3 trials and long-term extension studies for RA patients treated with tofacitinib, the incidence rate for severe infections has been estimated to be $\sim$2.7 per 100 patient-years, which is on par with those for biologics currently used in clinical practice for the treatment of RA [79]. While it appears that tofacitinib is associated with a higher risk of herpes zoster infection compared with biologics, this is usually mild and limited to a single dermatotome [80]. Herpes zoster infection with tofacitinib was more common in Asia and in people who were on concomitant glucocorticosteroids at baseline [79]. The frequency of malignancies (other than non-melanoma skin cancer) remained stable over time, despite increased exposure to tofacitinib, and was within the same range observed for RA treated with biologics [81].

Cardiovascular risk was one of the concerns raised about JAKinibs, largely related to the alterations in lipid profile noted with this class of drugs. Long-term data are reassuring thus far. In RA patients treated with tofacitinib, lipids were generally increased in the first 3 months of treatment, but stabilized thereafter [82]. This alteration was not associated with an increase in major adverse cardiovascular events, the incidence rates of which were comparable to those for placebo in the clinical trials and not increased in long-term extension studies [82]. Furthermore, the low-density lipoprotein (LDL): high-density lipoprotein (HDL) ratio remained generally stable after 24 months [79, 82]. In psoriasis patients, it seems that while there are increases in the total cholesterol, LDL and HDL levels, the total cholesterol : HDL ratio remains stable, the number of the more atherogenic small dense LDL particles does not change [83] and the incidence rates of major adverse cardiovascular events remains low [84]. Long-term data will, however, be required to reassure and inform use in patients already at a high baseline risk of cardiovascular events.

The data for tuberculosis (TB) are limited and are again obtained largely from tofacitinib studies [85]. Of patients with latent TB treated with isoniazid prophylaxis, there are no reported cases of active TB. As with biologic drugs, the frequency of TB was found to be increased in geographical regions with high background TB prevalence. The data so far do not allow sufficient risk comparison for TB between the various biologics and JAKinibs.

Laboratory abnormalities seen during treatment with tofacitinib include decreases in the numbers of neutrophils, lymphocytes, NK cells and platelets, as well as increased transaminases and serum creatinine levels. However, these alterations are usually mild and reversible [86]. Haemoglobin levels may be found to be increased. Pooled data from phase 3 and long-term extension studies showed that haemoglobin levels were initially increased and then were stabilized for up to 66 months of treatment with tofacitinib. Additionally, an inverse association was observed between increase in haemoglobin and disease activity, as assessed by ESR and CRP. Thus, it seems that reduction in systemic inflammation counterbalances the minor negative effects of tofacitinib in erythropoiesis. In addition, tofacitinib is a JAK3/JAK1 inhibitor with a limited effect on JAK2, which is used by erythropoietin [87]. The baricitinib trials in RA indicate that it has a similar safety profile to that of tofacitinib, although laboratory aberrancies might be slightly different, with more stable lymphocyte and platelet counts and a greater decrease in haemoglobin levels [86]. The latter could be explained by an inhibitory effect of baricitinib on JAK2. However, data obtained from phase 2, phase 3 and ongoing open-label extension studies suggest that reduction in haemoglobin levels is dose-dependent, being more pronounced in patients treated with 8 mg of baricitinib once daily, and only rarely being clinically significant or leading to treatment discontinuation [88–90]. Furthermore, it seems that counteracting mechanisms diminish this reduction in haemoglobin levels, over time [88].

Small decreases in neutrophil levels and increases in serum creatinine have been observed [89, 91]. Increases in LDL and HDL levels are stabilized after 3 months of

treatment, and the LDL: HDL cholesterol ratio remains stable [92]. The risk of herpes zoster infection with baricitinib appears to be comparable with that observed for tofacitinib [86], although a recent study suggests that this might be lower [89].

For other JAKinibs, data are less robust and further studies are needed to define their safety profile. Data for peficitinib are very limited, but it seems that the data are largely similar to those for tofacitinib [93, 94]. Interestingly, the side-effect profile for decernotinib appears comparable with those observed for other JAKinibs, despite decernotinib being a selective JAK3 inhibitor, which might therefore be predicted to have fewer off-target side effects [95–97]. Furthermore, as a potent CYP3A4 inhibitor, with potential to affect the metabolism of many other drugs, serious concerns have been raised [1, 98]. A developmental program for solcitinib, a selective JAK1 inhibitor, has been discontinued because of severe side effects, including serious but reversible derangement of liver function tests and adverse reactions [Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome] to the drug [99].

Safety data for upadacitinib appear similar to those for tofacitinib, although haemoglobin was found to be decreased with high doses [100, 101]. The early data suggest that filgotinib appears to have a slightly different safety profile in relation to the laboratory abnormalities. No increase in liver function tests or decrease in haemoglobin levels or number of lymphocytes or NK cells was observed in the trials conducted for RA patients [102, 103]. Additionally, despite the fact that both LDL and HDL were increased during treatment with filgotinib, the LDL:HDL ratio fell [102, 104]. Further studies are needed to confirm these findings. The degree of class effect and drug specificity relating to adverse events of JAKinibs remains to be determined.

Future perspectives and conclusion

Given the wide range of effector molecules that use the JAK/STAT pathway, the latter is increasingly an attractive therapeutic target for a wide range of immune-mediated diseases beyond RA. Further to those outlined in this review, isolated reports of other immune-mediated conditions treated with JAK inhibitors have been published and will undoubtedly continue to appear in the literature [105–107]. Phase 1 and phase 2 clinical trials are underway for SLE (NCT02535689, NCT03159936, NCT03288324, NCT03134222, NCT02708095 and NCT03285711), SSc (NCT03274076), SS (NCT03100942) and DM (NCT03002649). The efficacy and safety profiles of JAKinibs have not always corresponded with the effects predicted based on our understanding of the JAK/STAT pathways and selectivity of these drugs. By corollary, the relative risk between agents, and within their respective dose ranges have not yet been established. Long-term extension studies and rigorous post-market surveillance will be key to defining the safety profile for this category of drugs, particularly with the variety of new and more selective JAK inhibitors likely to reach the clinic in the next few years. The position of the JAKinibs in the treatment algorithms for inflammatory arthritis and other immune-mediated diseases remains to be defined.

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