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JAK inhibitors for the treatment of autoimmune and inflammatory diseases

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ABSTRACT

Cytokines play a central role in the pathophysiology of autoimmune and inflammatory diseases. Several cytokines signal through the JAK-STAT pathway, which is now recognized as a major target to inhibit the effect of a wide array of cytokines. JAK inhibitors are increasingly used in the setting of inflammatory and autoimmune diseases. While the currently approved drugs are panJAK inhibitors, more selective small molecules are being developed and tested in various rheumatic disorders. In this extensive review, we present evidence- or hypothesis-based perspectives for these drugs in various rheumatologic conditions, such as rheumatoid arthritis, systemic lupus erythematosus, giant cell arteritis, and autoinflammatory diseases.

1. Introduction

Cytokines are key mediators of inflammation and play a central role in the pathophysiology of autoimmune and inflammatory diseases [1]. Thus, cytokine inhibition is becoming increasingly used in immunology and rheumatology clinical practice [2]. Monoclonal antibodies are currently the most targeted therapies to effectively block either the cytokines directly or their receptors, and inhibit their uncontrolled effect. It is now recognized that the intracellular components of cytokine signaling, especially the Janus kinase (JAK) family of non-receptor tyrosine kinases that transduce signals, may be targeted to inhibit the effect of a wide array of cytokines [2–7]. Some JAK inhibitors are approved by the FDA/EMA for the treatment of rheumatoid arthritis, psoriatic arthritis, and inflammatory bowel disease. In addition, some data indicate that JAK inhibitors may be effective at treating other inflammatory/autoimmune diseases. While the currently approved drugs are panJAK inhibitors, more selective small molecules are being developed and tested in various inflammatory diseases. In this review, we analyze the data that have led to FDA/EMA approval of JAK inhibitors and present evidence- or hypothesis-based perspectives for these drugs in other inflammatory/autoimmune conditions.

2. JAK inhibition

The effect of a large number of cytokines relies on their binding to transmembrane receptors with intrinsic kinase domains such as those that bind receptor tyrosine kinases [8–10]. In mammals, the JAK-STAT (Signal Transducers and Activators of Transcription) pathways include four JAKs (JAK1–3 and tyrosine kinase 2, TYK2) and seven STATs (STAT1-5a/b, 6) [6,11]. When activated by cytokines, JAK phosphotransferases auto/transphosphorylate each other's tyrosine residues as well as the intracellular tail of the receptor subunits, enabling docking and recruitment of downstream signaling molecules, such as the STATs. STAT phosphorylation by JAKs leads to their hetero- or homodimerization and translocation into the nucleus (Fig. 1) [12]. Nuclear accumulation of STATs and binding to their cognate promoter elements regulate the transcription of target genes. Each cytokine receptor recruits a specific combination of JAKs/STATs to activate different programs in cells (Fig. 2) [6,11]. The array of STAT dimerization increases the range of gene-specific binding sites, contributes to the efficiency of nuclear translocation, and finally to variable biologic responses. These different combinations and preferentially employed JAKs have a crucial impact on therapeutic drug development and applications. Inhibiting a specific JAK may impede more than one pathway, explaining both the efficacy and adverse effects observed with JAK inhibitors.

The rationale for using JAK inhibitors to treat inflammatory and autoimmune diseases relies on the central role of cytokines in their pathogenesis [1]. Importantly, rheumatologic diseases are often marked by a cytokine profile (and thus by preferential activation of cytokine signaling pathways), leading to cytokine-targeted therapeutic

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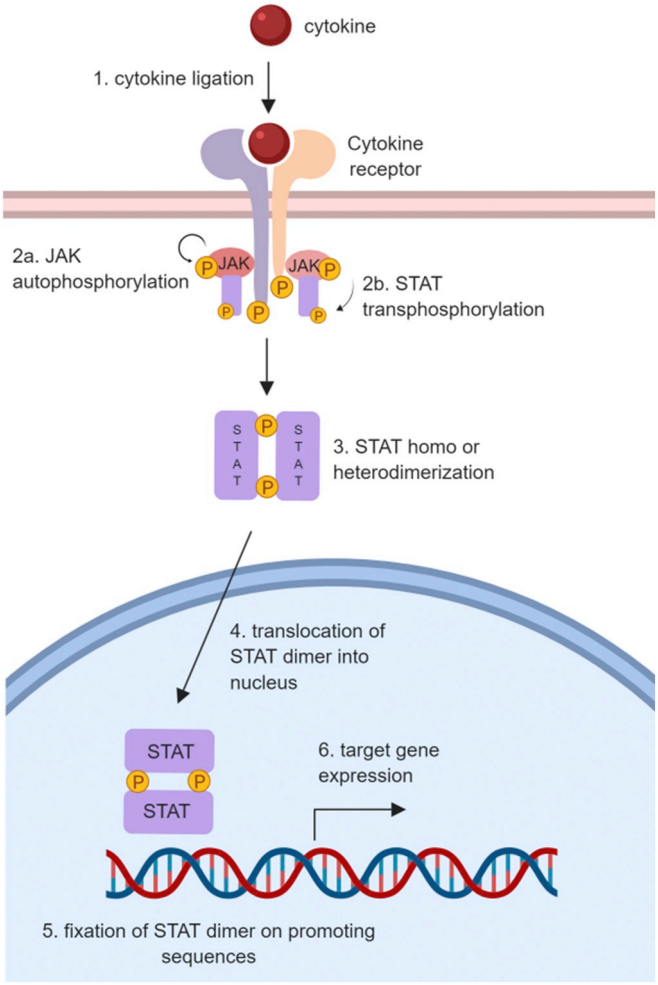

Fig. 1. The JAK-STAT signaling pathway. When activated by cytokines, JAKs phosphorylate the intracellular tail of the receptor subunits, enabling docking and recruitment of downstream STATs. STAT phosphorylation leads to their hetero- or homodimerization and translocation into the nucleus where they bind their cognate promoter elements to regulate the transcription of target genes.

strategies [2,3,6,8,10]. In this context, targeting all JAKs or different JAK combinations by small-molecule inhibitors is considered a relevant strategy. Apart from basic research, the pivotal role of JAKs was first established after the characterization of JAK3 as a key regulator of lymphocytes, leading to the development of tofacitinib [13–15]. Subsequently, the identification of a link between JAKs and cancer (e.g. gain-of-function (GOF) mutations in the JAK2 kinase-like domain associated with myeloproliferative diseases) [16–18] and the association between JAK polymorphisms and a variety of human diseases (e. g. JAK1 and juvenile idiopathic arthritis, TYK2 and lupus, inflammatory bowel diseases, psoriasis, multiple sclerosis, systemic sclerosis, inflammatory myopathies, primary biliary cirrhosis, and type 1 diabetes) have increased interest in the JAK-STAT pathway [19,20]. Three JAK inhibitors have now been approved for clinical use in humans in the USA and Europe: tofacitinib, which inhibits JAK1 and 3; baricitinib, which inhibits JAK1 and 2; and ruxolitinib, which inhibits JAK1 and 2. In addition, several clinical trials are currently underway, using either panJAK inhibitors (i.e. *first-generation* inhibitors, which demonstrate activity against three or four of the JAK family members) or next-generation selective JAK inhibitors (visit *www.clinicaltrials.gov*).

3. JAK inhibition in autoimmune diseases

3.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting the joints and leading to progressive articular damage, functional loss, and comorbidity [21]. A hallmark of RA is the presence of antibodies directed against citrullinated peptides and against immunoglobulin G, also known as rheumatoid factor [22]. The etiology of RA is still unknown but the pathophysiology is thought to involve a defect in genes encoding MHC class II molecules, especially HLA-DRB1, which is implicated in T-cell recognition of autoreactive peptide, as well as co-stimulatory pathways, including the interleukin (IL)-6 receptor, post-translational modification enzymes, and intracellular regulatory pathways (such as PTPN22, STAT3, or TNFAIP3) [21,23]. These modifications lower the threshold for immune activation and environmental factors or micro-trauma are suspected to promote disease onset and progression. A wide array of cytokines have been implicated in the pathophysiology of RA, including tumor necrosis factor (TNF)-α, IL-1, IL-6, IL-7, IL-15, IL-17, IL-18, IL-21, IL-23, IL-32, IL-33, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [23]. Nevertheless, therapeutic strategies targeting some of these, such as IL-1, IL-18, or IL-17 have shown little or no clinical benefit. On the other hand, blocking TNF-α or IL-6 was successful at inducing disease remission. Moreover, methotrexate (MTX), which inhibits lymphocyte proliferation and production of proinflammatory cytokines, is a well-established first-line treatment for RA [24]. Given the modulation of JAK-STAT by MTX and the success of the IL-6 receptor inhibitor tocilizumab, JAK1, JAK2, and TYK have emerged as new options for the treatment of RA [25]. The results of various clinical trials using tofacitinib in patients with RA have been reported worldwide [26–28]. Tofacitinib was the first JAK inhibitor approved by the FDA and EMA for patients with moderate to severe RA failing initial treatment with MTX or other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and poor prognostic factors. Tofacitinib as monotherapy or in combination with MTX has been shown to be effective with a clinical response similar to or better than that of TNF-α antagonists [26–28]. Tofacitinib has a rapid onset of action with an ACR20 response obtained in 2–4 weeks in combination therapy with MTX. After 6 months, three-quarters of patients receiving tofacitinib monotherapy had an ACR20 response and 55% had an ACR50 response. Tofacitinib had a prolonged effect, generally sustained for at least 72 months. No study has compared tofacitinib monotherapy with tofacitinib + csDMARD combination therapy.

Subsequently, a JAK1/JAK2 inhibitor, baricitinib, was approved by the EMA and FDA for the treatment of RA. Baricitinib has proven therapeutic superiority over placebo and over the TNF-α antagonist adalimumab in patients with an inappropriate response to MTX [29,30]. Baricitinib was significantly superior to placebo after 1 week and to adalimumab after 2–4 weeks. In the RA-BEGIN study, baricitinib monotherapy did not appear to be inferior to baricitinib + MTX combination therapy [31]. These effects were sustained or improved at week 52.

Upadacitinib is an orally administered JAK inhibitor with greater selectivity for JAK1 than for other JAKs. Upadacitinib was reported to improve RA signs and symptoms in patients with an inadequate response to MTX or a TNF-α antagonist in two phase 2 studies and one phase 3 study [32–34]. In the latter (SELECT-BEYOND) study, upadacitinib was tested against placebo in patients with active RA and a previous inadequate response or intolerance to biologic DMARDs, and receiving concomitant background csDMARDs [35]. Upadacitinib led to a rapid and significant improvement compared to placebo (56–65% ACR20 response vs. 28%, respectively; $p < .0001$) over 12 weeks in patients with refractory RA.

Filgotinib, a selective inhibitor targeting JAK1, has proven efficacy in several phase 2 studies [36,37]. In the DARWIN 2 study, which

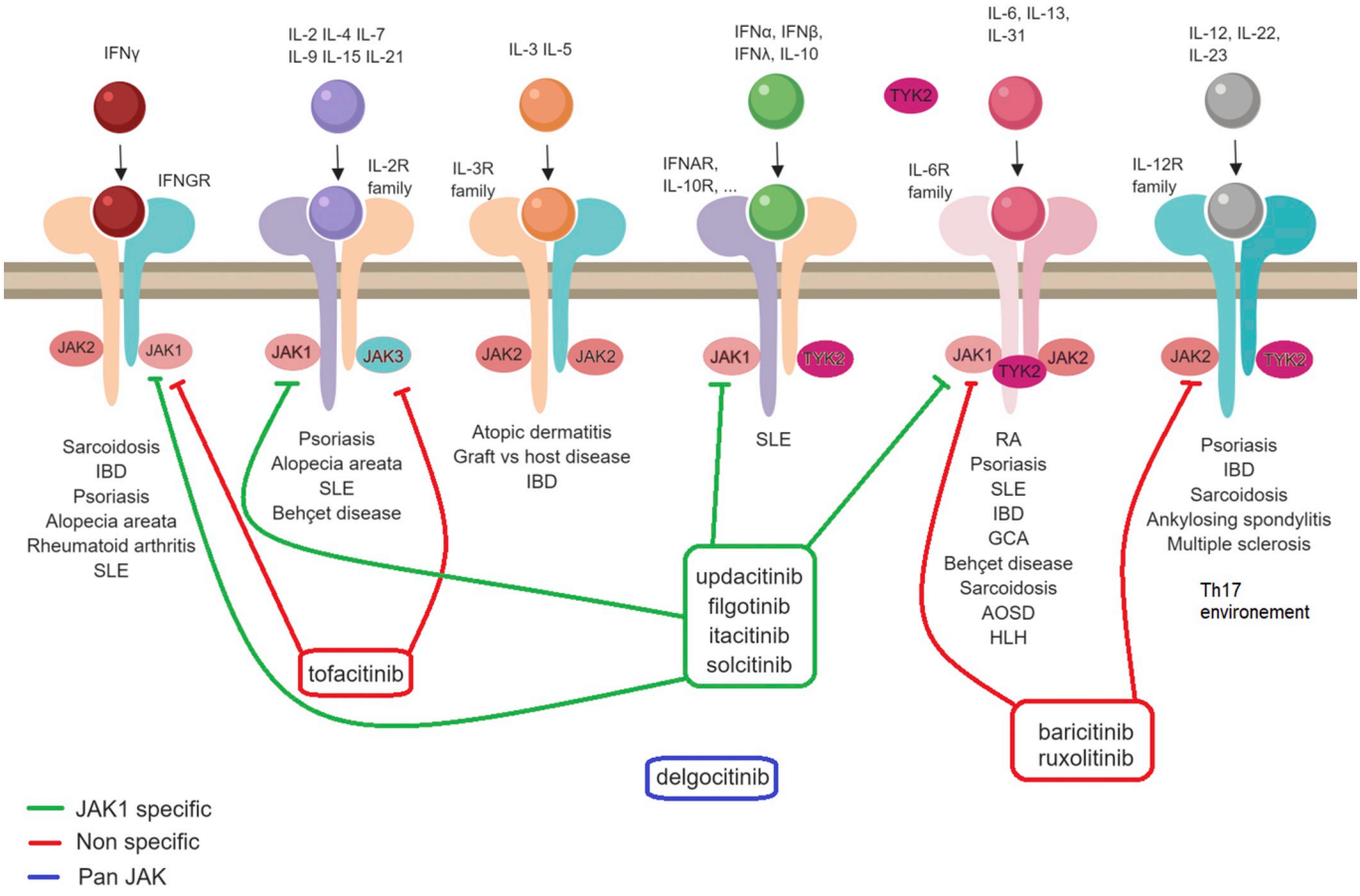

Fig. 2. Cytokines signaling network through JAK-STAT. Each cytokine receptor recruits a specific combination of JAKs/STATs to activate different programs in cells. The array of STAT dimerization increases the range of gene-specific binding sites, contributes to the efficiency of nuclear translocation, and finally to variable biologic responses. Inhibiting a specific JAK may impede more than one pathway, explaining both the efficacy and adverse effects observed with JAK inhibitors.

included 283 patients with moderately to severely active RA, significantly more patients receiving filgotinib at any dose achieved an ACR20 response vs. placebo (≥65% vs. 29%, respectively; $p < .001$) at week 12. Rapid onset of action was observed for most efficacy endpoints and responses were maintained or improved through week 24 [38]. Phase 3 studies of filgotinib are ongoing and other JAK inhibitors are currently being tested in the setting of RA.

3.2. Psoriatic arthritis and psoriasis

3.2.1. Psoriatic arthritis

Psoriatic arthritis (PsA) is a chronic, immune-mediated inflammatory arthritis causing progressive and irreversible structural damage to the joints and altered quality of life [39,40]. Up to 42% of patients with psoriasis are estimated to develop PsA after 10 years. The exact pathogenic mechanism leading to this disease is still not completely understood. There is now enough evidence to support a role of IL-23, IL-17, IL-22, IL-15, interferon (IFN)-γ, Th-17 cells, Th-22 cells, and TGF-β1 in the pathogenesis of the disease [41,42]. Most of the cytokines involved in PsA pathogenesis signal through the JAK-STAT pathway. Although IL-17 does not employ the JAK-STAT pathway, IL-23, an upstream driver of IL-17A release, exerts its function through the JAK2/TYK2-STAT3/STAT4 system [43]. Some studies have also shown that the JAK1-STAT1/STAT3/STAT5 network drives the expansion of Th17 and Treg cells via proinflammatory cytokines, such as IL-6, IL-23, and IL1β [44]. In vitro experiments and animal models have further implicated the JAK-STAT pathway as a major mediator of inflammation in PsA [42].

Tofacitinib has been approved in the EU and USA for use in combination with MTX in adult patients with active PsA who have had an inadequate response or were intolerant to previous DMARD therapy. The therapeutic efficacy of tofacitinib has been evaluated in two randomized, multinational, double-blind, placebo-controlled phase 3 trials (i.e. OPAL Broaden and OPAL Beyond studies) [45,46]. Pooled data from these studies have been analyzed; a total of 710 patients were included [47]. Patients had active PsA and either an inadequate response to ≥ 1 csDMARD and were TNF inhibitor-naïve (OPAL Broaden), or had an inadequate response to ≥ 1 TNF inhibitor (OPAL Beyond). Patients received either 5 or 10 mg tofacitinib twice daily (BID; to month 6) or placebo (to month 3; patients then switched to tofacitinib 5 or 10 mg BID). Patients also received one background csDMARD. Primary endpoints (i.e. ACR20 response and change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at month 3) showed significant improvements in patients receiving tofacitinib 5 or 10 mg BID vs. placebo. Significant improvements in HAQ-DI response, painful and swollen joints, psoriasis, enthesitis, and dactylitis vs. placebo were observed for both tofacitinib doses at month 3. Of note, significant differences in ACR20 rates were observed as early as week 2. For both doses, efficacy was maintained at month 6. Although not designed for this purpose, both tofacitinib-treated groups showed similar efficacy to the adalimumab group. At month 12, >90% of the patients across the tofacitinib groups met the criteria for radiographic non-progression in the joints.

Other JAK inhibitors, some being more specific for JAK1 (e.g. upadacitinib, filgotinib), are currently being tested for the treatment of PsA in phase 2 or phase 3 clinical trials.

3.2.2. Psoriasis

Psoriasis vulgaris is a chronic, immune-mediated, inflammatory, polygenic skin disorder affecting approximately 2% of the population. The disease is characterized by red, itchy, and scaly skin lesions located most commonly in the knees, elbows, scalp, and trunk. Disease severity is generally scored using the Psoriasis Area and Severity Index (PASI), with response rates expressed as percentages in clinical trials. The pathogenesis of the disease mostly relies on deregulation of immune cells, such as dendritic cells, Th17, and Th1 cells, and keratinocytes. Increased levels of TNF-α, IFN-γ, IL-2, IL-6, IL-8, IL-18, IL-22, and IL-17 have been reported in patients with psoriasis [48]. As for PsA, multiple cytokines use the JAK-STAT network (i.e. IL-23, IL-22, IL-15, and IFN-γ) offering relevant targets to JAK inhibitors. Nevertheless, the FDA has declined to approve tofacitinib for psoriasis.

Two large phase 3 studies (OPT Pivotal 1 and OPT Pivotal 2), with similar protocols, have been performed to assess the efficacy of tofacitinib in patients with moderate to severe chronic plaque psoriasis [49,50]. Patients who received tofacitinib (5 or 10 mg, BID), achieved PASI75 at week 16 in significantly higher percentages compared to those who received placebo. Clinical responses were sustained until month 24. Improvement in nail psoriasis was also observed after week 16 [51]. Another phase 3 trial, assessed the non-inferiority of tofacitinib vs. etanercept over 12 weeks (evaluated by PASI75 and Physician Global Assessment), and showed that tofacitinib 10 mg BID, but not 5 mg BID, was not inferior to etanercept [52]. An additional phase 3 trial showed that tofacitinib withdrawal may lead to psoriasis flare in >50% of cases, with efficacy recovered on retreatment in two-thirds of patients [53]. A phase 2 trial of baricitinib reported significantly higher PASI75 response rates at week 12 vs. placebo, with a sustained response to week 24 [54].

As for PsA, many other JAK inhibitors (either JAK-specific or not) are currently being tested in the setting of psoriasis (e.g. solcitinib, itacitinib).

3.3. Other immune-mediated skin diseases

JAK inhibitors have also been shown to be effective in other skin diseases, such as alopecia areata, vitiligo, and atopic dermatitis. Positive effects have also been reported in discoid lupus erythematosus, dermatomyositis, and other immune-mediated skin diseases.

3.3.1. Alopecia areata

Alopecia areata (AA) is an autoimmune disease characterized pathologically by autoreactive CD8+ T-cell and natural killer (NK) cell attack of the hair follicles leading to premature follicular senescence and sudden onset of hair loss in circular areas of the scalp or body [55,56]. Patients often have a family history of AA, atopy, or other autoimmune disease. Up-regulation of many IFN-regulated genes and cytokines has been reported, such as IFN-γ, IL-2, IL-2Ra, IL-21, and IL-15 [55]. IL-2 and IL-15 signal through the JAK1/JAK3 pathway while IFN-γ signals through JAK1/JAK2. JAK1 is thus considered as the target of choice in AA. The oral JAK1/JAK2 inhibitors ruxolitinib and baricitinib have been shown to induce hair regrowth in patients with AA [57,58]. Likewise, 3-month treatment with oral tofacitinib induced hair regrowth in about two-thirds of adolescent and adult patients with AA in open label and retrospective studies [59]. However, the disease relapsed when treatment was discontinued. Currently, both tofacitinib and ruxolitinib are in phase 2 trials for the topical treatment of AA.

3.3.2. Vitiligo

Vitiligo is a common chronic acquired disease of pigmentation [60]. Its etiology is unknown, but it is characterized by the destruction of melanocytes in the skin causing hypopigmented macules with sharply demarcated margins. The pathogenesis of vitiligo is still poorly understood, although most evidence indicates melanocyte destruction by cytotoxic T-lymphocytes [61]. The central cytokine involved in vitiligo seems to be IFN-γ, which signals through JAK1/JAK2 [61–63]. A retrospective case series of 10 patients treated with tofacitinib for ≥3 months with concomitant light exposure reported repigmentation in 50% of patients [64]. Repigmentation was mostly observed in the sun-exposed skin areas. In a non-randomized case series of patients with vitiligo treated with topical ruxolitinib (1.5%) for 20 weeks, all 11 patients had a statistically significant mean improvement in Vitiligo Area Scoring Index score [65]. The most significant repigmentation was seen on the face while repigmentation of vitiligo patches located on the trunk or lower extremities was not reported. As in AA, the majority of the pigment that returned during treatment with JAK inhibitors was not sustained after treatment discontinuation.

3.3.3. Atopic dermatitis

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease characterized by highly pruritic recurrent eczematous lesions with a strong alteration of quality of life. AD is a heterogeneous disease triggered by environmental factors in genetically susceptible hosts. Lesional skin contains elevated levels of pro-inflammatory cytokines, including IL-4, IL-5, IL-13, IL-31, IL-22, and IFN-γ [66]. The IL-4/IL-13 inhibitor dupilumab has recently been approved by the FDA and EMA for clinical use in adults with moderate to severe AD [67].

A phase 2 study was performed with topical tofacitinib in mild to moderate AD with promising results [68]. The Eczema Area and Severity Index (EASI) was significantly improved within 1 week and pruritus in only 2 days. Oral tofacitinib has also been evaluated in an open study of six patients with moderate to severe AD with promising efficacy [69]. Oral baricitinib was shown to be effective in a phase 2 trial of 124 adults with moderate to severe AD [70]. The improvements in EASI50 by baricitinib vs. placebo were significant as early as week 4. Upadacitinib has been tested in a phase 2b dose-ranging study in 167 adults with moderate to severe AD [71]. A reduction in pruritus was noted at week 1 and improvement in the extent and severity of skin lesions at week 2, for all dosages. At week 16, there was a significant reduction in EASI in the treated group compared to the placebo group (74% vs. 23%, respectively). Results of a phase 2b randomized, dose-ranging trial evaluating topical ruxolitinib in 307 adult patients with mild to moderate AD compared with triamcinolone (0.1%) and vehicle showed a significant benefit over vehicle control (i.e. EASI improvement at week 4: 71.6% vs. 15.5%, respectively; $p < .001$) [71]. A phase 2 study of topical delgocitinib, a nonselective topical JAK inhibitor, in 327 AD patients reported a significant improvement in modified EASI at week 4 weeks vs. placebo (73% vs. 12%, respectively) [72].

Other oral and topical JAK inhibitors, either selective or not, are currently being tested in patients with AD [71].

3.3.4. Discoid lupus erythematosus

Discoid lupus erythematosus (DLE) is the most prominent form of cutaneous lupus erythematosus (82%). Discoid lesions are classically distributed over sun-exposed areas and include atrophy, follicular prominence, telangiectasia, and disc-like plaques [73]. Pathologic results show interface dermatitis with vacuolar degeneration of the basal cell layer and necrotic keratinocytes. DLE pathogenesis mostly involves type-I IFNs (IFN-α and IFN-β, whose levels correlate with disease severity) and plasmacytoid dendritic cells (pDCs) [74]. Type-I IFNs are responsible for stimulating the expression of TNF-related apoptosis-inducing ligand (TRAIL), apoptosis receptor CD95, cytotoxic proteins, and death receptors involved in apoptotic pathways [75,76]. Basic studies have produced contrasting data on the role of IFN-γ, IL-17, and IL-22, and the production of CD4+ T-cells in DLE. Nevertheless, there is evidence that targeting IFN-γ and the Th1 immune response could be relevant in the treatment of DLE [77,78].

Multiple studies using lupus-prone mouse models have provided evidence of the benefit of inhibiting JAKs on autoantibody levels, lupus nephritis, and lupus-like skin manifestations [74,79,80]. Of note, the development of R333, a topical JAK/SYK inhibitor for DLE, was

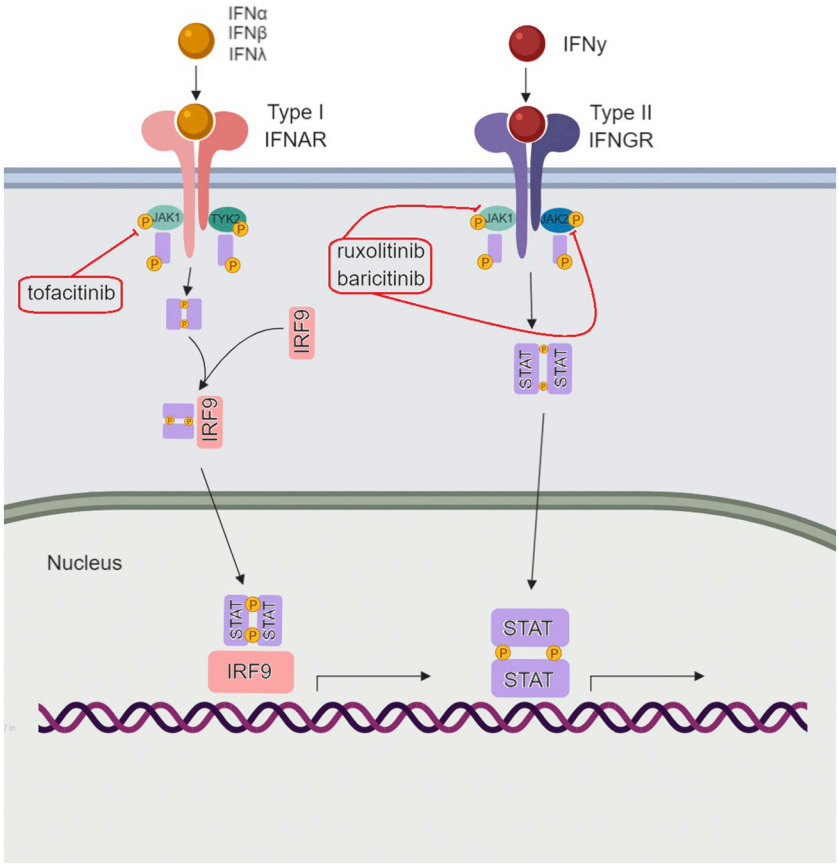

Fig. 3. The IFN signaling pathway. The binding of IFNs to their specific receptor triggers the activation of JAKs and the subsequent phosphorylation of STATs. For type-1 IFN, the recruitment of IRF9 leads to the formation a transcriptional complex that culminates in upregulation of interferon-stimulated genes (ISGs).

stopped in 2013 following insufficient results of a phase 2 study (unpublished) [80]. Recently, the results of a phase 2 clinical trial of baricitinib (either 2 or 4 mg/day) vs. placebo in patients with active systemic lupus erythematosus (SLE) involving the skin or joints have been published [81]. Compared with the placebo group, there was a slight but significant improvement in the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) in the group receiving 2 mg (+1.1 over placebo; $p = .037$) but not in the group receiving 4 mg (+0.5 over placebo; $p = .33$). These encouraging results support the use of JAK inhibitors as a promising treatment option in DLE.

3.3.5. Dermatomyositis

Dermatomyositis (DM) is an autoimmune disease characterized by muscular inflammation, skin involvement and frequent systemic manifestations, including vasculopathy, interstitial lung disease, and subcutaneous calcifications. Type-I IFNs, arising from pDC activation through Toll-like receptors (TLR)-7 and −9, contribute to DM pathogenesis by inducing proinflammatory cytokines and activating the JAK-STAT pathway [75,82]. A feed-forward loop, where type-I IFNs stimulate pDCs and further perpetuate the immune response, is also suspected. Furthermore, muscular overexpression of STAT1 has been reported in DM patients. STAT3 is also able to translocate into the mitochondria and may be involved in the regulation of mitochondrial calcium release, a process potentially important for calcification in DM. Several case reports have suggested the efficacy of JAK inhibitors in refractory DM [83–86]. One patient with refractory DM and concurrent myelofibrosis improved significantly while on ruxolitinib [83]. A case series of three patients with multidrug-resistant DM treated with tofacitinib reported a significant improvement in their Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) [87]. In an additional case report, the authors reported the improvement of cutaneous manifestations, muscle strength, and arthritis in a patient with DM treated with tofacitinib [88]. Another 32-year-old patient presenting with refractory anti-MDA-5-positive DM with interstitial pulmonary involvement who had a clear IFN signature was treated with tofacitinib and experienced a significant increase in physical performance, an ameliorated skin condition, and morphologically improved interstitial lung disease [85].

Finally, a fast and persistent response of extensive and rapidly progressive DM-associated calcifications in two patients treated with tofacitinib was reported [86]. In both patients there were no new calcifications and existing calcifications were either regressive or stable. Moreover, concomitant life-threatening DM-associated interstitial lung disease rapidly responded to tofacitinib monotherapy in one patient. These results pave the way to a wider use of JAK inhibitors in refractory DM.

3.3.6. Miscellaneous

A few studies have shown that the JAK-STAT pathway is involved in the pathogenesis of other skin diseases for which JAK inhibitors may constitute new therapeutic options.

Juczynska et al. reported on the expression of the JAK-STAT signaling pathway in bullous pemphigoid and dermatitis herpetiformis [89]. In a hypothesis letter, Soheil Tavakolpour also proposed tofacitinib as a potentially effective drug to treat pemphigus, on the basis of the critical role of cytokines such as IL-4 and IL-21 in the development of pemphigus [90]. Dees et al. demonstrated that JAK-2 is activated in a TGF-β-dependent manner in systemic sclerosis [91,92]. Subsequently, Deverapalli et al. reported a great improvement in joint and skin manifestations in a 27-year-old patient with refractory systemic sclerosis treated with tofacitinib [93]. Rang Kim et al. also reported on two patients with generalized deep morphea and eosinophilic fasciitis

treated with tofacitinib in combination with prednisone and low-dose MTX [94]. Both patients underwent improvement and reversed prior pathology, even when prednisone failed to show a response. Concordant with these reports, five patients suffering from hypereosinophilic syndrome with skin involvement were successfully treated with tofacitinib or ruxolitinib either alone (4/5) or with low-dose steroids (1/5) [95]. Finally, several retrospective studies evaluating the efficacy of ruxolitinib given as salvage therapy for steroid-refractory graft-versus-host disease involving the skin have shown promising response rates, ranging from 45 to 80% [96,97].

3.4. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a complex, prototypic autoimmune disease characterized by an unpredictable course with periods of flares and remission. The pathogenesis of SLE involves defective apoptosis and clearance of apoptotic materials and immune complexes by macrophages and the complement system, impaired clearance of neutrophil extracellular traps, increased pro-inflammatory Th17 response, and defective regulation by Tregs and Bregs [74]. In addition, pDCs are stimulated by excessive apoptotic materials and immune complexes to produce IFN-α and IL-6 through interaction with TLR-7 and -9. The rationale for targeting the IFN pathway in SLE and especially through JAK inhibition has been reviewed recently (Fig. 3) [74]. Briefly, in patients with active SLE the levels of many cytokines are abnormal, including IFNs (α and γ), IL-2, IL-6, IL-10, IL-12, IL-15, IL-17, IL-21, IL-23, and B-cell activation factor (BAFF) [98]. Genome-wide association studies in SLE have identified varied gene polymorphisms within the *IL12B*, *IL10*, *JAK2*, *TYK2*, and *STAT4* gene loci [99]. Moreover, *IRF5* and *IRF8* genes along with SOCS1 and STAT3 proteins seem to play an important role in the pathophysiology of SLE. The importance of IFNs and the JAK-STAT pathway has further been confirmed in lupus-prone mice. Treatments with tofacitinib or ruxolitinib resulted in improved levels of SLE activity markers (decreased cytokines and antibody production, increased complement levels) as well as decreased lupus manifestations (nephritis, skin lesions) and prolonged survival [100]. Human ex-vivo studies have demonstrated the prominent role of the IFN-JAK-STAT network in SLE by showing overexpression of INF-related genes, JAK1, JAK2, STAT1, and STAT2 in CD3+ T-cells. Moreover, STAT1 was overexpressed in SLE patient Tregs and CD4+ T-cells, and its expression was correlated with SLE severity [101,102]. Finally, the production of autoantibodies by B-cells was abrogated in vitro by adding the JAK1/2 inhibitor ruxolitinib + STAT3 inhibitor to the culture system [103].

In 2016, Wenzel et al. reported the case of a 69-year-old woman with chilblain lupus successfully treated with ruxolitinib prescribed for concurrent myelofibrosis [104]. Skin lesions relapsed after treatment discontinuation but complete resolution of skin lesions occurred after re-challenge with ruxolitinib.

These results have led to clinical trials of JAK inhibitors in human SLE. Recently, the first double-blind, randomized, placebo-controlled, phase 2 trial has evaluated baricitinib in adult patients with non-severe non-renal SLE [81]. A total of 314 patients with active joint or skin disease were included. Patients were randomly assigned to receive baricitinib 2 mg/day or 4 mg/day or placebo for 24 weeks in addition to standard of care therapy. At week 24, the proportion of patients with resolution of arthritis or skin lesions was significantly higher in the baricitinib 4 mg group than in the placebo group ($p = .04$). SLE Responder Index-4 (SRI-4) was also achieved in a significantly higher percentage of patients receiving baricitinib 4 mg (64% vs. 48% placebo; $p = .02$). Although the reduction of joint tenderness with baricitinib was moderate, the study provides encouraging results for further phase III clinical trials.

Of note, a phase 2 trial of solcitinib, a selective JAK1 inhibitor, in patients with SLE was terminated prematurely due to a lack of efficacy in the interim data analysis along with the occurrence of two cases of drug reactions with eosinophilia and systemic symptoms (DRESS) syndrome and four cases of reversible liver toxicity.

3.5. Primary Sjogren's syndrome

Primary Sjögren's syndrome (pSS) is a complex autoimmune disease characterized by lymphocytic infiltrates of the salivary and lacrimal glands, resulting in Sicca syndrome. Autoantibodies against SSA/Ro and SSB/La antigens are hallmarks of pSS [105]. The pathogenesis of pSS is poorly understood but a number of gene loci have been linked to pSS, including polymorphisms in *IRF5*, *STAT4,* and *IL12A* [106,107]. These polymorphisms are speculated to confer a susceptibility favoring increased IFN responses in pSS. The expression of type-I IFN-inducible genes in pSS also positively correlates with titers of anti-SSA/Ro and anti-SSB/La autoantibodies [108]. Moreover, the IFN signature was associated with higher disease activity index scores. pDCs are the major source of type-I IFN production and activated pDCs are detected in minor salivary gland biopsies from patients with pSS [109]. Studies of peripheral blood cells from pSS patients have found altered STAT3 and STAT5 phosphorylation, but increased phosphorylation of STAT1 Y701 upon stimulation with IFN-α, IFN-γ, and IL-6 [110]. Further analyses revealed that the type-I IFN signature involved the TLR7/9-STAT3 pathway [111]. Mice models (with deletion of IκB-ζ or its transcriptional regulator STAT3 in epithelial tissues) have to some extent reinforced the role of IFN-JAK-STAT in the pathophysiology of pSS [112].

Topical tofacitinib has been tested in phase 2 randomized, controlled trials of dry eye disease [113,114]. The treatment improved signs and symptoms of dry eye while reducing conjunctival cell surface expression of HLA-DR, corneal infiltration of CD11+ cells, and corneal expression of proinflammatory cytokines (TNF-α, IL-23, IL-17A).

4. JAK inhibition in inflammatory diseases

4.1. Inflammatory bowel diseases

Inflammatory bowel diseases (IBDs), comprising ulcerative colitis (UC) and Crohn's disease (CD), are chronic and relapsing immune-mediated conditions of the gastrointestinal tract caused by a deregulated mucosal immune response to intestinal flora in genetically predisposed individuals [115]. UC and CD have differing clinical signs and pathologic features. Both IBDs share gut microbial abnormalities, but whether dysbiosis is a primary or secondary phenomenon in immune disorders is still a matter of debate. Biological therapies targeting TNF-α, IL-12/23, and gut integrins have revolutionized the treatment of IBDs, but these drugs are not universally effective. Genome-wide association studies have reported an association between CD and polymorphisms in genes encoding JAK2, STAT3, TYK2, and the IL-23 receptor [116,117]. About 30% of CD-associated gene polymorphisms are shared with UC, including *IL23R*. In addition, various cytokines, including IL-12, IL-17, IL-18, IL-21, IL-22, IL-23, IL-27, IL-32, and IFN-γ, seem to play an important role in CD pathogenesis [118]. While blood levels of IL-8 are elevated in both CD and UC patients, IFN-γ, IL-6, and IL-7 are more specific for CD. Such a cytokine profile is associated with predominant Th1/Th17 immune responses [119]. Conversely, UC patients have elevated IL-5, IL-13, IL-15, and IL-33, consistent with a predominant Th2 response.

The first IBD phase 2 study of a JAK inhibitor tested tofacitinib for the treatment of moderate to severe UC [120]. A clinical response at week 8 occurred significantly more often in the 15 mg/day treatment group compared to placebo (78% vs. 42%, respectively; $p < .001$). Subsequently, two phase 3 induction studies (OCTAVE 1, OCTAVE 2) and one maintenance study (OCTAVE Sustain) reported higher remission rates at week 8 and after 52 weeks in the tofacitinib-treated group vs. placebo (18.5% vs. 8.2%, respectively, $p = .007$ in OCTAVE 1; 16.6% vs. 3.6%, respectively, $p < .001$ in OCTAVE 2; 40.6% vs. 11.1%, respectively, $p < .001$ in OCTAVE Sustain) [121]. Mucosal healing

rates, a major treatment outcome in IBD, were also higher in the treatment groups in these studies. In 2018, the FDA and the EMA approved the use of tofacitinib in patients with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. Curiously, results from a phase 2b study of tofacitinib for the treatment of CD were less encouraging [122]. No significant differences in clinical response or remission rates were observed after 8 weeks. Two phase 2b studies of tofacitinib for induction and maintenance therapy of CD also failed to reach their primary endpoint despite a longer treatment duration [123]. These results may be due to high placebo response rates (up to 37%) or differences in the immunopathogenesis between CD and UC.

Conversely to panJAK inhibitors, selective inhibitors showed positive clinical outcomes in CD in phase 2 trials (upadacitinib and filgotinib) and phase 3 trials are currently recruiting. Filgotinib has been evaluated for the treatment of moderate to severe CD in a randomized phase 2 clinical trial in 174 patients (FITZROY study) [124]. Clinical remission at week 10 was more frequently obtained in the treatment group vs. placebo (47% vs. 23%, respectively; $p = .008$). Interestingly, this efficacy was independent of prior anti-TNF exposure. In the 20-week maintenance study, 71% of the initial responders had sustained clinical remission and 79% had a clinical response, while maintaining an improvement in quality of life. A recent phase 2 study (CELEST study) evaluated upadacitinib efficacy in patients with moderate to severe CD and showed significantly more clinical response and endoscopic improvement in the upadacitinib-treated group vs. placebo at week 16, with a dose-dependent response [125].

Head to head trials comparing JAK inhibitors to current biologic agents in IBD are the next step in the development of these new molecules and will precise their place in the therapeutic armamentarium.

4.2. Ankylosing spondylitis

Ankylosing spondylitis (AS) is a chronic inflammatory arthritis of the spine and sacroiliac joints frequently associated with extra-articular manifestations, such as acute anterior uveitis. The disease has a strong association with HLA-B27 inheritance and belongs to the group of spondyloarthritis, which includes PsA, IBD-related arthritis, and reactive arthritis. Genome-wide association studies have identified a number of susceptibility variants in AS, including *HLA-B27*, *IL23R*, *IL1A,* and *IL12R, JAK2, TYK2,* and *STAT3* variants [126–128]. The IL-23/IL-17 axis is strongly implicated in the pathogenesis of AS. Cell-mediated mechanisms have been described for CD4+ and CD8+ T-cells, mucosal-associated invariant T-cells, γδ T-cells and innate-lymphoid cells resulting in a Th17 response and further release of cytokines, including TNF-α, IL-22, IL 17, IFN-γ, IL-26, and GM-CSF [129]. Biologics targeting TNF-α and IL-17 have been approved for clinical use in AS.

A recent 16-week phase 2 dose-ranging trial has assessed the efficacy of tofacitinib in TNF inhibitor-naïve patients with active AS [130]. Compared with placebo, significantly higher rates of patients on 5 mg tofacitinib BID achieved the primary end-point (ASAS20) at week 12 (80.8% vs. 41.2%, respectively; $p < .001$). Patients on all doses of tofacitinib achieved most of the secondary end-points, including ASAS40, BASDAI50, improvement of Spondyloarthritis Research Consortium of Canada spine scores, and quality of life indices. Further studies are required in order to assess JAK inhibitor efficacy over a longer follow-up period, and phase 2 studies are underway to evaluate the efficacy of upadacitinib and filgotinib in AS.

5. The future of JAK inhibition

5.1. Ocular diseases

Uveitis is defined as inflammation of the iris, ciliary body, vitreous, retina and/or choroid [131]. >60 causes of uveitis have been described and can be classified into five groups including pure ophthalmologic entities, infectious diseases, masquerade syndromes, drug-related uveitis, and autoimmune/inflammatory diseases, which account for about one-third of cases [132,133]. Around 40% of cases of uveitis remain idiopathic. Pro-inflammatory IL-1, IL-2, IL-6, IFN-γ, and TNF-α have all been detected within ocular fluids from the inflamed eye together with IL-4, IL-5, IL-10, and TGF-β [134]. The levels of IL-17 in aqueous humor correlate significantly with disease activity in patients with idiopathic anterior acute uveitis, while the level of IFN-γ in aqueous humor correlates significantly with disease activity in patients with HLA-B27-associated uveitis [135]. IL-17-expressing T-cells are substantially elevated in the blood of patients with active uveitis, suggesting the possible involvement of Th17 cells. Expression of IL-23, IL-1R1, and IL-17R was elevated in the vitreous of patients with uveitis [136]. Interestingly, mice with targeted deletion of STAT3 in the CD4+ T-cell compartment are resistant to the development of experimental autoimmune uveitis [137]. Furthermore, topical administration of a mimetic peptide of the suppressor of cytokine signaling-1 (SOCS1, which inhibits JAK2 and TYK2) decreases ocular inflammation and mitigates ocular disease during mouse experimental uveitis [138]. In an experimental autoimmune uveitis model, topical treatment with tofacitinib suppressed the expression of many inflammatory chemokines and chemokine receptors in ocular tissues, and reduced immune cell infiltration and subsequent tissue damage in rodents [139]. Recently, Paley et al. described two patients with refractory anterior uveitis or scleritis, who could not tolerate csDMARDs or the TNF inhibitor adalimumab, and whose ocular disease improved with tofacitinib treatment [140]. Nevertheless, both were treated with concurrent MTX and the exact effect of tofacitinib remains difficult to establish. A phase 2 clinical trial is currently underway to assess the efficacy of oral filgotinib in patients with non-infectious uveitis. Finally, Sarny et al. described the case of a 51-year-old man with a long-term history of devastating mucous membrane pemphigoid who had received several lines of immunosuppressive therapies (including MTX, mycophenolate mofetyl, cyclophosphamide, rituximab) and whose condition stabilized after the initiation of oral baricitinib [141]. Further studies will be necessary to determine the potential effect of JAK inhibitors in this autoimmune disease of unknown etiology.

5.2. Giant cell arteritis

Vasculitides comprise a collection of autoimmune diseases that affect blood vessels, with giant cell arteritis (GCA) being the most common form of vasculitis [142,143]. Most cytokines implicated in the pathogenesis of GCA, including IL-6, IL-12, IFN-γ, (IL-17) and IL-23, signal through the JAK-STAT pathway [142]. Th1 and Th17 responses have been identified as key regulators in vasculitis lesions of GCA [144]. In addition, Tregs appear to play an important role in GCA pathogenesis; these are decreased in the blood and arterial lesions of patients with GCA. Using a model of experimentally-induced vasculitis of human temporal arteries grafted in immunodeficient mice, Hartmann et al. found high levels of expression of STAT1 in arteritis tissue lesions [145]. IFN-γ, the major inducer of STAT1, was 10-fold higher in GCA patients compared to controls. Administration of tofacitinib prevented Th1 cell accumulation in the vessel walls and reduced IFN-γ, IL-17, and IL-21 production [146]. Tofacitinib disrupted adventitial microvascular angiogenesis, reduced outgrowth of hyperplastic intima, and minimized tissue-resident memory T-cells.

One phase 2 trial of baricitinib and one phase 3 trial of upadacitinib in patients with relapsing GCA are currently underway and the early results of these trials are promising. Due to the close association between GCA and polymyalgia rheumatica, it is possible that JAK inhibitors might be part of the therapeutic strategy of this disease in the future.

5.3. Sarcoidosis

Sarcoidosis is a systemic granulomatous disease that can involve any organ although the lungs and lymphatic system are the most commonly affected [147]. There is evidence that the JAK-STAT network plays a role in the pathogenesis of sarcoidosis [148]. Activation of macrophages within granulomas has long been depicted as dependent on a predominant Th1 response. Indeed, granuloma formation is dependent on various cytokines, including TNF-α, IL-12, IL-1, IL-16, and IL-23 [147]. TNF-α is critical for granuloma formation through the recruitment of naïve T-cells and by promoting pro-inflammatory Th1 polarization. Th1 cells undergo oligoclonal expansion and produce INF-γ. The combined use of surface markers and functional assays to study CD4+ T-cells in sarcoidosis has revealed a marked expansion of Th17.1 cells, a subset that only produces IFN-γ [149,150]. IFN-γ activates the JAK-STAT pathway, resulting in up-regulation of STAT1 transcriptional targets. Several studies have shown that the STAT1 signature is characteristic of the transcriptome in mononuclear cells and tissues of sarcoidosis patients [151,152]. Rotenberg et al. have reported the dramatic improvement of refractory skin, nasosinusal and pulmonary sarcoidosis with ruxolitinib treatment given for concurrent JAK2-mutated polycythemia [153]. Several treatments have been tested successively over an 18-year period (including MTX, azathioprine, leflunomide, infliximab, and adalimumab), but had to be stopped due to either a lack of efficacy or adverse effects. After 3 months, skin lesions disappeared *ad integrum*, lung infiltrations decreased dramatically and pulmonary function tests improved dramatically. At the same time, Damsky et al. reported the case of a 48-year-old woman who had sarcoidosis with pulmonary involvement and treatment-resistant skin lesions [154]. Over a period of 8 years, her skin disease was resistant to topical glucocorticoids, minocycline, hydroxychloroquine, MTX, adalimumab, tacrolimus, and apremilast. Tofacitinib treatment resulted in abatement of her skin lesions, along with decreased tissue mRNA expression of JAK-STAT-dependent (IFN-γ, IL-6) and -independent markers (TNF-α, mTORC1, IL1B, IL12B, IL18). Such data pave the way to targeting the JAK-STAT pathway in sarcoidosis.

5.4. JAK inhibitors in autoinflammation

5.4.1. Type-1 interferonopathies

Interferonopathies are a subset of autoinflammatory disorders unified by a prominent type-I IFN gene signature [155–157]. They represent a heterogeneous group encompassing phenotypically different diseases, such as Aicardi-Goutières syndromes 1–7, inherited chilblain lupus [158], Stimulator of Interferon gene-associated Vasculopathy with onset in Infancy (SAVI), Singleton Merten syndrome, or Proteasome-Associated Autoinflammatory Syndromes/Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature (PRAAS/CANDLE). Interferonopathies are Mendelian disorders that present early in life with fevers, sterile organ inflammation and a high type-I IFN response gene signature in peripheral blood cells. Binding of type-1 IFN to its receptor triggers the activation of JAK1 and TYK2, subsequent phosphorylation of STAT1 and STAT2, and recruitment of IRF9 to form a transcriptional complex, namely ISGF3. This complex translocates to the nucleus to promote IFN-stimulated gene expression (Fig. 4). This transcriptional response is further amplified through a feed-forward amplification loop. The group led by Goldbach-Mansky recently reported on 18 patients severely affected with CANDLE ($n = 10$), SAVI ($n = 4$), or other presumed interferonopathies (n = 4) in an expanded access program with baracitinib (dose optimization protocol) [159,160]. All patients had failed with the use of 1–6 conventional and/or biologic DMARDs and 78% were on chronic steroid treatment. Most of the patients in this study showed significant improvements in efficacy measures (clinical signs and symptoms, reduction in steroid treatment, quality of life, and IFN biomarker reduction) and 50% of the CANDLE patients had durable remission allowing steroid discontinuation. CANDLE patients showed more improvement than SAVI and other patients. Such differences suggest a disease-specific responsiveness that may elucidate previously unappreciated subtleties in IFN signaling. Of note, higher doses of baricitinib were required to control the symptoms in these patients and treatment was often associated with infections, presumably related to over-immunosuppression.

Other case reports or case-series involving patients with interferonopathies have been published; three patients with SAVI were successfully treated with ruxolitinib [161], two patients with familial chilblain lupus due to a STING GOF mutation had clinical improvement with tofacitinib [158], while another case was successfully treated with ruxolitinib, two patients with Aicardi-Goutières seemed to have a positive response with ruxolitinib.

5.4.2. STAT1 and STAT3 GOF-associated diseases

Autosomal dominant GOF mutations in *STAT1* cause a variable clinical phenotype including chronic mucocutaneous candidiasis, susceptibility to dimorphic fungal and invasive viral infections, combined immunodeficiency, autoinflammation, and organ-specific autoimmunity [162]. *STAT3* GOF mutations cause early-onset lymphoproliferation with lymphadenopathy, hepatosplenomegaly and multiorgan autoimmunity, including cytopenias, hepatitis, inflammatory lung disease, enteropathy, hypothyroidism, and diabetes mellitus [163]. Treatment of *STAT1* or *STAT3* GOF-associated diseases is challenging because many patients fail to respond to multiple immunosuppressive therapies. Forbes et al. described 17 patients (STAT1 GOF, $n = 11$; STAT3 GOF, $n = 6$) [164] who received either tofacitinib (n = 1) or ruxolitinib ($n = 16$); STAT3 GOF patients received adjunct tocilizumab. Fourteen patients had significant clinical improvement with the addition of tofacitinib or ruxolitinib to their therapy, sometimes with dramatic efficacy. Long-term treatment led to sustained clinical improvement, mostly effective on immune dysregulation features. There were few medication side-effects and most patients tolerated the inhibitor well. Three patients did not respond to JAK inhibition, ultimately succumbing to fatal disease progression.

5.4.3. Systemic juvenile idiopathic arthritis, adult-onset Still's disease, and hemophagocytic lymphohistiocytosis

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease and is defined as arthritis of unknown etiology occurring in patients aged ≤16-years which persists for at least 6 weeks, other conditions being excluded [165]. JIA is actually a group of inflammatory disorders comprising seven mutually exclusive categories: systemic arthritis, persistent or extended oligoarthritis, polyarthritis rheumatoid factor (RF)-negative, polyarthritis RF-positive, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis. Given the proximity of some of these categories to their adult counterparts, tofacitinib has been evaluated in a phase 1, open-label, multicenter study of pediatric patients with active polyarticular course JIA (extended oligoarthritis, RF-positive or -negative, psoriatic arthritis, or enthesitis-related arthritis) [166]. Patients with systemic JIA, persistent oligoarthritis or undifferentiated JIA were excluded from the study. Beyond pharmacokinetic data, the trial revealed that tofacitinib was well tolerated and caused no serious adverse events. A phase 3, open-label, follow-up, long-term extension safety study is ongoing. In addition, the efficacy and safety of tofacitinib are being evaluated in a 44-week, phase 3, randomized withdrawal, double-blind placebo-controlled study in pediatric patients with JIA. A third study is also planned to evaluate tofacitinib in pediatric patients with systemic JIA.

In the setting of JIA, systemic JIA (SJIA) represents one particular category because it is now considered to belong to a continuum of disease with adult-onset Still's disease (AOSD) [167–169]. SJIA and AOSD share common clinical and pathophysiological features, with IL-1 and IL-18 being the pivotal cytokines involved in their pathogenesis. Nevertheless, IL-6 and IFN-γ, two cytokines signaling through JAK-

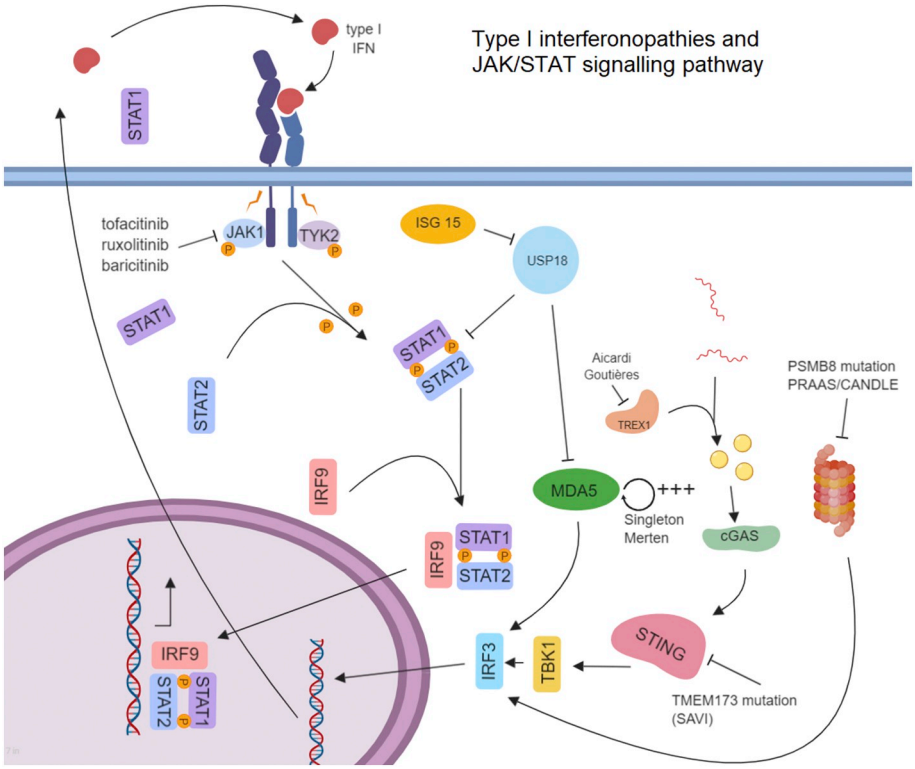

Fig. 4. Type-1 IFN signaling pathway and interferonopathies. Monogenic interferonopathies are due to loss-of-function mutations leading to increased cytosolic DNA (e.g. TREX1) or RNA sensing; or gain-of-function mutations leading to constitutive activation of cytosolic IFN signaling pathways (e.g. STING, MDA5); or loss-of-function mutations in inhibitors of the IFN-α receptor (IFNAR; e.g. ISG15, USP18); or proteasomal dysfunction leading to increased IFN signaling through increased cellular stress (e.g. PSMB8).

STAT, also represent key mediators of inflammation in both diseases. Although no data are available in the setting of AOSD, Huang et al. have recently described the case of a 13-year-old girl with refractory SJIA treated with tofacitinib [170]. The disease had been present for 2 years and was characterized by polyarticular arthritis, fever, and lymphadenopathy. She had a minimal response to steroids, csDMARDs, and etanercept, and presented osteoporotic vertebral fracture and gastritis that were considered to be steroid-associated side-effects. Since her family refused parenteral treatments, she was started on oral tofacitinib, 5 mg BID. Her arthritis improved steadily over the next 2 months, while acute-phase reactants and serum ferritin returned to normal. Complete remission was achieved after 3 months and was sustained at 6 months, when she was able to discontinue steroids for the first time since the onset of SJIA. Of note, tofacitinib interruption was marked by arthritis recurrence but retreatment led to complete resolution.

Both SJIA and AOSD are associated with the frequent occurrence of macrophage activation syndrome, now preferentially termed reactive hemophagocytic lymphohistiocytosis (reHLH) [168]. The key cytokine involved in reHLH pathophysiology is IFN-γ, which is produced by cytotoxic lymphocytes and promotes aberrant macrophage activation. Apart from SJIA and AOSD, there is evidence that JAK inhibition constitutes a therapeutic option in HLH. In murine models of primary and secondary (reactive) HLH, treatment with ruxolitinib not only prevented HLH but also significantly prolonged mice survival [171]. Subsequently, the first reports of patients treated with ruxolitinib for reHLH were published in 2017 [172,173]. A 38-year-old woman presented with severe EBV-related reHLH refractory to dexamethasone, intravenous immunoglobulin, etoposide, and rituximab [172]. Ruxolitinib was started as a salvage therapy. Following initiation, several disease markers improved (i.e. serum ferritin, lactate dehydrogenase, fibrinogen, and liver function tests). However, her pancytopenia did not recover and she died after 7 days due to cerebral hemorrhage and candidemia. At the same time, an 11-year-old boy with refractory HLH of unknown etiology dramatically responded to ruxolitinib 2.5 mg BID, while he had deteriorated with dexamethasone, etoposide, and anakinra [173]. After remission was obtained, the patient underwent bone marrow transplantation and is currently well.

Several clinical trials (phases 1, 2, and 3) of ruxolitinib for the treatment of HLH or reHLH are currently recruiting patients.

5.4.4. *Periodic fevers: FMF, TRAPS, MKD, and HA20*

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory syndrome worldwide. It is characterized by recurrent, self-limited episodes of fever and polyserositis accompanied by elevation of acute-phase reactants [174]. FMF is most often inherited in a recessive manner and the majority of FMF patients have bi-allelic mutations in the *MEFV* gene, which encodes an inflammasome sensor named pyrin [175]. Since the inflammasome is the central player in the IL-1/IL-18 pathway, targeting JAK-STAT could be beneficial in FMF. Indeed, IL-1 and IL-18 receptors activate IRAK family proteins through MyD88 to finally activate the NFκB transcription factor. Two case reports have been published claiming successful treatment of FMF with tofacitinib [176,177]. Nevertheless, both were questionable because: (i) in one case the identified mutation E148Q was heterozygous and is considered of unknown significance rendering the diagnosis of FMF uncertain [176]; and (ii) in the other case the patient was receiving tofacitinib for concurrent RA, which may have been responsible for the improvement of symptoms with tofacitinib [177]. Thus, the pathogenic link describing the indication of JAK inhibitors in FMF treatment is still missing.

TNF receptor-associated periodic syndrome (TRAPS) is clinically characterized by recurrent episodes of long-lasting fever and systemic inflammation. To date, no patient with TRAPS has been treated with tofacitinib. Indeed, TNF-α does not signal through the JAK-STAT pathway. However, one mutation (c.262 T > C; S59P) in the *TNFRSF1A* gene was shown to induce constitutive activation of TNF-R1, along with IL-1β, MAPK, and SRC/JAK/STAT3 pathways [178]. In addition, stimulation of cells carrying the S59P mutation by exogenous IL-1β induced a significant and persistent enhancement of IL-6 and IL-8. It is therefore tempting to hypothesize that tofacitinib could be beneficial to certain subsets of TRAPS patients.

Mevalonate kinase deficiency (MKD) typically presents with

recurrent self-limited bouts of multisystem inflammation that are characterized by fever, abdominal pain, cervical lymphadenopathy, rash, and arthralgia [174]. MKD is caused by recessively inherited mutations in the gene encoding mevalonate kinase, with the degree of residual enzyme activity largely determining disease severity. Due to the clinical manifestations and prominent role of IL-1 in disease pathogenesis, MKD is considered as an autoinflammatory syndrome. During attacks, patients with MKD have increased levels of cytokines such as TNF-α, IL-1β, IL-6, and IFN-γ. In addition, a multiomics approach performed in two siblings with MKD, one being asymptomatic and the other presenting all the classical characteristics of the disease, led to the identification of a missense mutation in *STAT1* in the symptomatic patient [179]. This GOF variant was involved in increased activation of the JAK-STAT pathway, raising the hypothesis that this could constitute a therapeutic target in MKD.

Haploinsufficiency of A20 (HA20) is newly recognized genetic disorder characterized by autoinflammatory and autoimmune manifestations closely resembling Behçet's disease (BD) [180]. HA20 resembles BD with recurrent oral and genital ulcers, joint and skin involvement, and abdominal features. However, HA20 differs from classical BD because first symptoms occur in early childhood, recurrent fever is more common, HLA-B51 antigen is uncommon, and abdominal symptoms are over-represented. In addition, the response to colchicine in HA20 is inconsistent and unpredictable. The disease is due to an autosomal dominant inherited loss-of-function mutation in *TNFAIP3* coding A20, an important endogenous regulator of inflammation. Haploinsufficiency of A20 results in increased NFκB signaling and reduced inhibition of the NLRP3 inflammasome and patients with HA20 have elevated levels of serum inflammatory cytokines, including IL-1β, IL-6, IL-17, IL-18, and TNF-α. In a murine experimental model ($A20^{-/-}$ mice), A20 negatively modulated STAT1-dependent gene transcription in myeloid cells by suppressing STAT1, both in unstimulated conditions and after IFN-γ or IL-6 stimulation [181]. The increase in *STAT1* gene transcription in the absence of A20 was shown to be JAK-STAT-dependent. Moreover, JAK inhibition in vivo resulted in significant reduction of enthesitis [181]. The authors thus speculate that JAK inhibitors may have a potential benefit in the treatment of enthesitis.

5.4.5. Behcet's disease

Behcet's disease (BD) is a recurrent systemic inflammatory disorder of unknown origin characterized by oral and genital ulcers, uveitis, and skin lesions [182]. Both CD4+ and CD8+ T-cells producing Th1 cytokines IL-2, IL-12, and IFN-γ are increased in the peripheral blood and inflammatory tissues in BD. Genetic studies have revealed upregulation of *IL-23R*, *IL-12R*, *JAK1*, *STAT3*, and *STAT4* genes in BD [182,183]. Moreover a recent transcriptome performed in cells from BD patients has showed upregulation of Th17-related genes and type I IFN-inducible genes with five clusters of genes enriched in T- and B-cell activation pathways and two clusters enriched in type-I IFN, JAK-STAT, and TLR signaling pathways [184]. The JAK1-STAT3 signaling pathway was activated in BD, possibly through the activation of Th1/Th17-type cytokines, such as IL-2, IFN-γ, IL-6, IL-17, and IL-23 [182,184,185]. Active BD is characterized by high serum levels of these cytokines, supporting the use of the IL-6 inhibitor tocilizumab or IL-12/23 inhibitor ustekinumab. Considering these data, some authors have proposed that tofacitinib may be a new therapeutic option for BD but, to date, there are no published case reports or ongoing clinical trials.

6. Safety

The use of JAK inhibitors is associated with an increased risk of serious infections and opportunistic infections [186–189]. These included pneumonia, upper respiratory tract infections, urinary tract infection, or gastroenteritis, along with tuberculosis, cellulitis, panniculitis, septic shock, and osteomyelitis [186]. BK viremia and BK nephropathy were reported in kidney transplant recipients treated with high-dose tofacitinib associated with other immunosuppressive drugs. One case of progressive multifocal leukoencephalopathy in a 75-year-old patient treated with ruxolitinib was also reported [187]. Overall, the incidence of infections was similar to that observed with other DMARDs [190]. A retrospective meta-analysis of pooled data from RA trials indicated a lower risk of infection in tofacitinib-treated patients than in patients treated with biologic DMARDs [191,192]. Only the risk of reactivation of varicella zoster virus was substantially higher in tofacitinib-treated patients [186,193]. Of note, monoclonal antibodies targeting IFN-α or its receptor (i.e. sifalimumab and anifrolumab) are also associated with an increased risk of herpes zoster. The combination of JAK inhibitor and steroids seems to further increase this risk [194]. It is therefore advisable to vaccinate patients against herpes zoster before starting immunosuppressive therapies.

There have been concerns that JAK inhibitors may increase the risk of malignancies [191]. To date, meta-analyses of patients included in clinical trials and extension studies have showed no significantly increased risk of malignancies or any specific type of malignancy in RA patients treated with either biologic DMARDs or tofacitinib compared to those treated with a placebo or csDMARDs [195,196].

Treatment with JAK inhibitors may cause changes in laboratory parameters, including levels of hemoglobin, decreased numbers of lymphocytes, NK cells, neutrophils, and platelets [186]. Depending on the targeted JAK, hemoglobin levels may either increase or decrease. Some of these changes may be transitory and none has been reported to be associated with serious infections or malignancy. In addition, elevation of liver transaminase, creatine kinase, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and creatinine levels are commonly observed in patients treated with JAK inhibitors [186]. Only a small proportion of the patients develop serious adverse events related to these changes and rheumatologists are advised to monitor these parameters regularly to detect patients with significant changes in these values and take appropriate measures.

Safety concerns have also been raised for venous thromboembolism and gastrointestinal perforation [186]. Such complications have been reported in patients treated with JAK inhibitors. Although data from pooled analyses seem reassuring, long-term observation in the real world is awaited to evaluate these risks.

7. Conclusion

There are now several FDA/EMA-licensed JAK inhibitors for the treatment of inflammatory and autoimmune diseases, and more are currently undergoing clinical trials. The results of these studies are eagerly awaited because they may broaden the use of JAK inhibitors to patients with refractory or difficult to treat rheumatologic disorders. At the same time, several new-generation JAK inhibitors are being developed with more selective effects on JAKs. These new inhibitors might alter treatment paradigms through a rapid dose-dependent action and fewer side-effects, and eventually also as monotherapy.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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