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Review

A review of JAK–STAT signalling in the pathogenesis of spondyloarthritis and the role of JAK inhibition

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Abstract

Spondyloarthritis (SpA) comprises a group of chronic inflammatory diseases with overlapping clinical, genetic and pathophysiological features including back pain, peripheral arthritis, psoriasis, enthesitis and dactylitis. Several cytokines are involved in the pathogenesis of SpA, variously contributing to each clinical manifestation. Many SpA-associated cytokines, including IL-23, IL-17, IL-6, type I/II interferon and tumour necrosis factor signal directly or indirectly via the Janus kinase (JAK)–signal transducer and activator of transcription pathway. JAK signalling also regulates development and maturation of cells of the innate and adaptive immune systems. Accordingly, disruption of this signalling pathway by small molecule oral JAK inhibitors can inhibit signalling implicated in SpA pathogenesis. Herein we discuss the role of JAK signalling in the pathogenesis of SpA and summarize the safety and efficacy of JAK inhibition by reference to relevant SpA clinical trials.

Key words: spondyloarthritis, Janus kinase inhibitor, AS, PsA

REVIEW

Rheumatology key messages

- Spondyloarthritis comprises a group of chronic inflammatory diseases with a complex pathophysiology.
- JAK inhibition may be able to block multiple cytokines involved in the pathogenesis of spondyloarthritis.
- Clinical trials of JAK inhibitors in patients with spondyloarthritis have shown favourable results.

Introduction

Spondyloarthritis (SpA) comprises a group of chronic inflammatory diseases with overlapping clinical, genetic and pathophysiological features that can include spinal inflammation, peripheral arthritis, enthesitis, dactylitis, skin and nail disease, uveitis and IBD [1, 2]. SpA can manifest as predominantly axial SpA (involving mainly the axial joints) or as predominantly peripheral SpA (affecting the peripheral joints, entheses, skin and nails). Axial SpA includes both ankylosing spondylitis (AS, i.e. radiographic axial SpA) and non-radiographic axial SpA [3–5] while peripheral SpA captures a number of SpA subsets, the most common of which is PsA [2, 3, 6]. Other SpA subsets include reactive arthritis and SpA related to IBD [1, 2]. The extra-articular manifestations of SpA, including IBD, anterior uveitis and psoriasis, may profoundly influence disease progression and therapy, and are a key consideration for SpA diagnosis and management.

In such a heterogeneous group of diseases, treatment selection reflects the dominant clinical manifestations. For active axial SpA and axial symptoms in PsA, physical therapy along with non-steroidal anti-inflammatory

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drugs (NSAIDs) is recommended as first-line treatment [4, 5]. On failure to control axial disease, most guidelines recommend that patients should progress to treatment with a biologic DMARD (bDMARD) such as a TNF or IL-17A inhibitor. For PsA with predominantly peripheral manifestations, treatment options can include non-biologic DMARDs such as methotrexate; bDMARDs such as TNF inhibitors, IL-17A inhibitors, IL-12/23 inhibitors, IL-23 (p19) inhibitors and abatacept; and oral small molecule inhibitors such as apremilast [7–9], with the recommended treatment based on the predominant manifestations and severity of disease. Currently, only TNF and IL-17A inhibitors are effective across both axial and peripheral SpA, and IL-17A inhibitors may not be appropriate in patients with non-musculoskeletal manifestations such as active IBD or active uveitis [7, 8]. There is therefore a need for new therapies that can effectively control the various manifestations of SpA, with JAK inhibitors recently being approved for active PsA and AS.

Despite the availability of bDMARDs, many patients fail to gain or maintain stringent treatment targets of low disease activity (which lacks an agreed definition) or inactive disease in SpA [10–14], highlighting an unmet need. Janus kinase (JAK) inhibitors are an emerging class of oral small molecule treatments that have demonstrated efficacy in SpA [15–21], with several molecules now approved or in late-phase clinical development. The aim of this review is to summarize the role of JAK–signal transducer and activator of transcription (STAT) signalling in the pathogenesis of SpA and review the evidence from clinical trials of JAK inhibitors in patients with SpA.

Disease pathogenesis of SpA

The exact aetiology and pathogenesis of SpA, particularly axial SpA, remain unknown. SpA likely arises from interaction between environmental and genetic components that elicit a chronic inflammatory response involving the innate and adaptive immune systems, interacting with exaggerated tissue damage repair [22–24]. There are several theories as to the triggering event(s), including mechanical stress at entheses, infection and dysbiosis in the gastrointestinal microbiome [23, 25–30].

Several alleles in the major histocompatibility complex may play a contributory role in the pathogenesis of SpA, although HLA-B27 has the strongest association across different SpA phenotypes [23, 31, 32]. Carriage of the HLA-B27 gene occurs with greater frequency in patients with SpA (AS: $\geq$90% of patients express HLA-B27; reactive arthritis: 60–90%; PsA or IBD: 50–60%) than in the general population ($<$8%) [23, 33, 34]. Other genetic risk factors have been demonstrated, with *IL23R*, *IL12B*, *IL1* and *TNF* polymorphisms associated with the development of AS and PsA, along with *RUNX3*, *ERAP1* and *TBX21* polymorphisms [35–41]. A genome-wide association study has also implicated the *IFIH1* locus as being associated with PsA [42]. Gain-of-function mutations in the *IFIH1* gene have subsequently been shown to be associated with a range of neuroinflammatory phenotypes, including enhanced JAK–STAT pathway activation [43].

Entheses are the insertion sites of tendons and ligaments to bone surfaces and are areas of high mechanical stress. In the absence of disease, a high number of transcortical microvessels (TCVs) enable communication between bone marrow and entheses [44]. However, under repeated biomechanical stress, vasodilation of TCVs occurs, which facilitates the efflux of innate immune cells from the peri-entheseal bone marrow directly into the enthesis [45–47]. In SpA, this mechanical stress is thought to be a driver for entheseal inflammation, and subsequent formation of enthesophytes and new bone formation [46, 48]. Differences may exist in how enthesitis manifests across SpA phenotypes; for example, enthesitis in PsA is characterized generally by more entheseal soft tissue inflammation or synovio-entheseal complex disease, whereas enthesitis in axial SpA is characterized more by peri-entheseal osteitis in the spine, which may suggest different immunopathogeneses for axial and peripheral disease, influenced by anatomical differences [47]. The sacroiliac joint and entheses both have fibrocartilage and the complex compression and shear forces transmitted to the bone at both sites may result in the commonality of pathology [49].

The immunopathogenesis of SpA is complex and involves immune cells of the innate immune system such as macrophages, innate lymphoid cells (ILCs) and dendritic cells as well as cells of the adaptive immune system including various subsets of T cells [50]. $CD4^+$ and $CD8^+$ T cells are known to be present in the enthesis, which is a key site of SpA pathogenesis [51]. In addition, several different cytokines are involved in the pathogenesis of SpA, as shown by inhibitors of TNF, IL-17A, IL-12/23 (p40) and IL-23 (p19), demonstrating efficacy in the treatment of axial SpA and/or PsA [7–9]. These cytokines are directly and indirectly affected by JAK molecules, and important distinctions are emerging with regard to which cytokines drive distinct clinical manifestations of SpA; treatment should therefore be tailored to the dominant domains in the individual patient [7–9]. A treatment option that targets multiple cytokines involved in SpA pathogenesis could therefore be a useful option in reducing inflammation across multiple disease manifestations.

Gut inflammation in patients with SpA is common, particularly in axial SpA, with an estimated 6–14% of patients with AS and 4% of patients with PsA having IBD, which is significantly more frequent than in the general population [52, 53]. In addition, microscopic, sub-clinical bowel inflammation has been found in approximately one-half of patients with SpA [54, 55]. Conversely, the prevalence of SpA in patients with IBD appears to be around 20% [56–58]. As a result, there has been much interest in the role of the microbiome in the development of SpA [59–62]. The gut microbiota

influences the balance between T cell subtypes (Th1, Th2, Th9, Th17 and regulatory T cells), which are essential in host defence against infection [63–65]. Dysbiosis and impairment of gut barrier function allow pathogenic bacteria to invade the gut lumen and promote overactivation of innate and adaptive immune responses, leading to an excess production of proinflammatory cytokines (TNF, IL-1, IL-23, IL-17A and IL-17F), which may contribute to the pathogenesis of SpA.

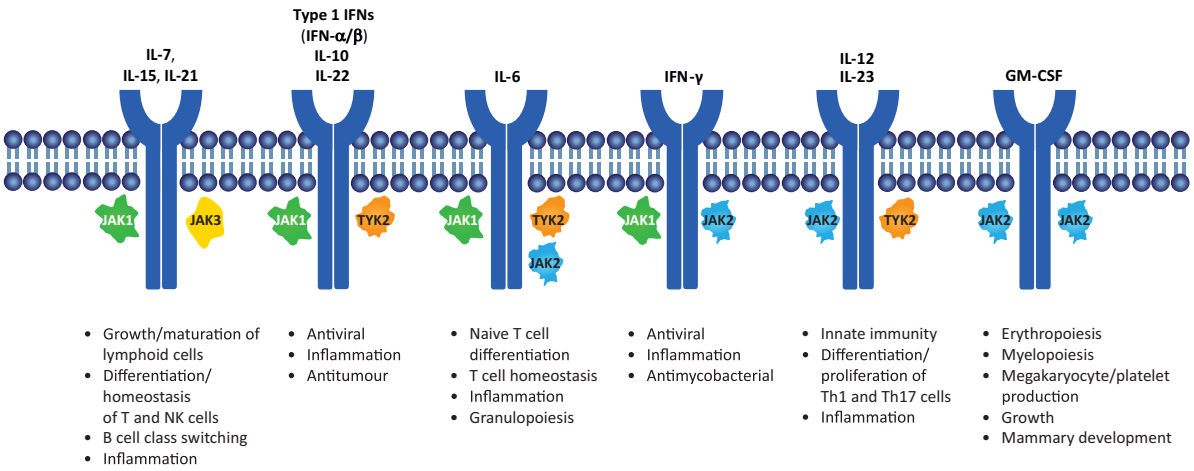
The JAK–STAT pathway

Cytokines signal through several different intracellular pathways, one of which is the JAK–STAT pathway [66–68]. In particular, cytokines that bind to type I/II cytokine receptors mediate their effects through activation of the JAK–STAT pathway [69, 70]. There are four members of the JAK family—JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2)—and each cytokine/growth factor receptor is associated with a pair of JAK family members required for downstream signalling [69, 71]. There are seven members of the STAT family, STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6, and through the activation of specific STAT family members by the JAK pairs associated with a particular receptor, transcription of specific genes is regulated.

Upon binding of cytokines to these receptors, JAK molecules (which are associated with the intracellular portion of the receptor) phosphorylate both themselves and the receptors [72]. STAT molecules are then able to bind to phosphorylated tyrosine residues on the receptors where they too are phosphorylated by JAKs. Once phosphorylated, STAT molecules dissociate from the receptors and can form homo- or heterodimers before migrating to the nucleus, where they regulate the expression of target genes [69, 71]. Regulation of gene expression involves recruitment of co-activators by the STAT dimers. These co-activators interact with the histone proteins with which nuclear DNA is associated, weakening the interactions between the histones and the DNA and making specific regions of the DNA more accessible to STATs and the nuclear transcriptional machinery [73, 74]. STAT molecules do not remain in an activated state but become dephosphorylated, with a half-life estimated in the region of 15–30 min, after which they dissociate from the DNA and are exported from the nucleus [75].

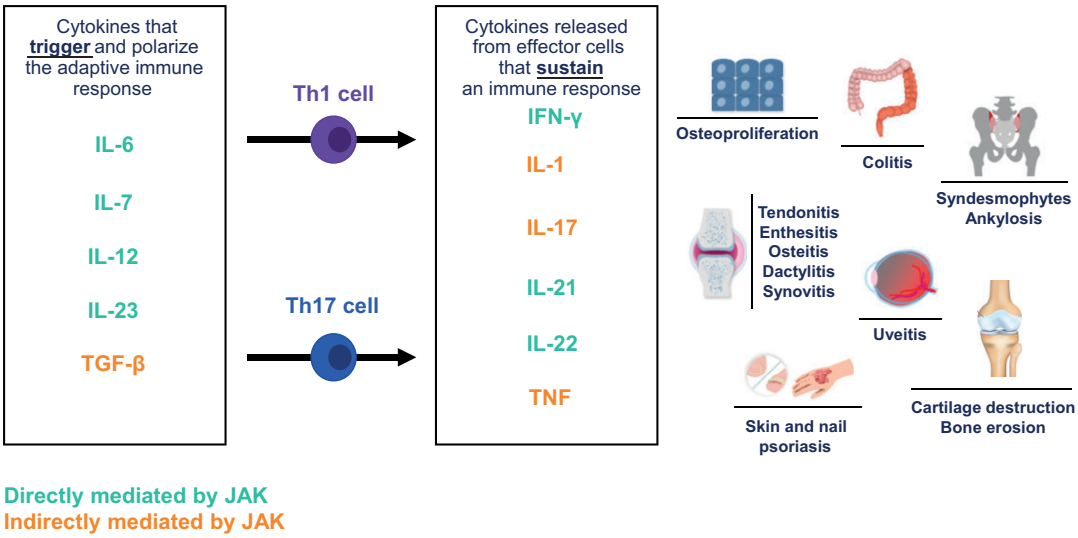
Each pair of JAK molecules can be associated with the regulation of different biological processes (Fig. 1). JAK1, in combination with JAK3, is involved in the signalling of common gamma chain cytokines such as IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 [69, 71]. These cytokines are involved in the growth/maturation of lymphoid cells and differentiation/homeostasis of T and natural killer cells [21, 50, 51, 76–78] (Fig. 1). IL-7, in particular, modulates ILCs, which are implicated in the pathophysiology of SpA [79]. JAK1 in combination with JAK2 and/or TYK regulates key proinflammatory cytokines such as IFN-γ and IL-6; IL-6 is also involved in ILC activation (Fig. 1) [21, 67, 80–83]. JAK2 and TYK2 regulate the signalling of IL-12 and IL-23, the latter of which can be produced by spinal entheseal soft tissue and adjacent bone anchorage sites, with these cytokines playing a key role in the differentiation of $CD4^+$ Th1 and Th17 cells, respectively [84]. Finally, JAK2 homodimers regulate signalling downstream of erythropoietin and thrombopoietin and therefore play a role in erythropoiesis, and may be involved in regulating myelopoiesis [81, 82]. JAK2 homodimers also signal downstream of granulocyte-macrophage colony-stimulating factor (GM-CSF), a cytokine that has recently been linked with the pathogenesis of SpA [85].

Fig. 1 JAK–STAT pathways mediate signalling for multiple cytokines, including those implicated in the pathogenesis of SpA [69–73]



GM-CSF: granulocyte-macrophage colony-stimulating factor; JAK: Janus kinase; NK: natural killer; SpA: spondyloarthritis; STAT: signal transducer and activator of transcription; TYK2: tyrosine kinase 2.

FIG. 2 JAK-dependent cytokines (directly and indirectly) mediate pathogenic pathways in SpA [50, 86–91]



JAK: Janus kinase; SpA: spondyloarthritis.

JAK inhibition is therefore likely to affect multiple cytokines involved in the pathogenesis of SpA.

In addition to direct inhibition of cytokine signalling, JAK inhibition can also have indirect effects on the production of key cytokines involved in the pathogenesis of SpA, including cytokines involved in triggering and sustaining the immune response (Fig. 2). As noted above, IL-23 signals through JAK2–TYK2 and is involved in the proliferation and differentiation of $CD4^+$ Th17 cells, which produce IL-17A [92–94]. In addition, IL-7 signals through JAK1–JAK3 and induces mucosa-associated invariant T cells to produce IL-17A [95]. Consequently, JAK inhibition may lead to indirect downstream inhibition of IL-17A production [21, 96]. IL-17A plays a key role in a number of clinical manifestations of SpA, as reflected by the efficacy of IL-17A inhibitors in both PsA and AS [5, 7, 9]. Interestingly, inhibition of IL-23 does not appear to be effective in the treatment of AS, which may be linked to IL-17 production that is independent of IL-23 and associated JAK pathway signalling [76, 97].

IL-12 also signals via JAK2–TYK2 (Fig. 1), and along with IFN-γ (via JAK1–JAK2) is essential for the production of TNF by macrophages [21]. TNF is another key cytokine in the pathogenesis of SpA and is involved across disease manifestations. Although TNF is not directly affected by JAK inhibition, blockade of JAK2–TYK2 or JAK1–JAK2 will ultimately modulate its production due to inhibition of IL-12 and IFN-γ production [21]. Recently plasmacytoid dendritic cells have been described at the human spinal enthesis that have inducible TNF and type 1 interferon protein production, which can be inhibited with the JAK inhibitor tofacitinib [98]. Finally, the synergistic activities of cytokines mean that inhibition of JAK-dependent cytokine receptors will reduce the potential cellular effect of other non-JAK-mediated effects (e.g. those mediated via IL-17 receptor A, IL-1 receptor or TNF receptor signalling).

Inhibition of the JAK–STAT pathway

Although bDMARDs demonstrate efficacy through blockade of individual cytokines (IL-23, IL-17A and TNF) [4, 5, 7–9], JAK inhibition is able to directly or indirectly block multiple cytokines involved in the pathogenesis of SpA (Fig. 2). There are four JAK inhibitors that are currently approved or are in late-phase development for SpA indications (Tables 1 and 2), each of which has differing levels of selectivity across the JAKs. One additional JAK inhibitor, baricitinib, is approved for the treatment of RA but is not currently in clinical development for SpA.

The selectivity of these JAK inhibitors has been assessed in various *in vitro* analyses. These include biochemical assays using recombinant JAK molecules and cellular assays in which cell lines or *ex vivo* preparations (e.g. human whole blood) are treated with JAK inhibitors and then stimulated with cytokines to assess the ability of JAK inhibitors to prevent STAT phosphorylation []. In these cellular assays, tofacitinib demonstrated preferential inhibition of JAK1 and JAK3, with 5- to 100-fold selectivity over JAK2 [103]. Filgotinib demonstrated a ~30-fold selectivity for JAK1- over JAK2-dependent signalling in cellular and whole blood assays [104]. Upadacitinib (UPA) was designed to have a greater selectivity for JAK1 *vs* JAK2, JAK3 and TYK2, demonstrating ~60-fold selectivity for JAK1 over JAK2 and >100-fold selectivity over JAK3 in cellular assays [105]. Finally, deucravacitinib is a potent inhibitor of TYK2 that has

Table 1 Summary of key trials of JAK inhibitors in development in AS

	Upadacitinib (SELECT-AXIS 1) [16]	Tofacitinib [99]	Tofacitinib [17]	Filgotinib (TORTUGA) [18]
Phase	2/3	2	3	2
Population	NSAID-IR	NSAID-IR	NSAID-IR	NSAID-IR
Treatment arms	UPA 15 mg QD Placebo	TOFA 2, 5 or 10 mg BID Placebo	TOFA 5 mg BID Placebo	FILG 200 mg QD Placebo
Primary study duration	14 weeks	12 weeks	16 weeks	12 weeks
Number of patients randomized	187	207	269	116
Primary endpoint	ASAS40 response at week 14	ASAS20 response at week 12 (predicted by Emax model)	ASAS20 at week 16	ΔASDAS at week 12
Results from primary endpoint(s)	UPA 15 mg *vs* placebo: 52% *vs* 26%, $P = 0.0003$	TOFA 2, 5, 10 mg *vs* placebo: 56%, 63%, 67% *vs* 40%	TOFA 5 mg *vs* placebo: 56% *vs* 29%, $P < 0.0001$	FILG 200 mg *vs* placebo: –1.47 *vs* –0.57, $P < 0.0001$

ASAS20: improvement of ≥20% and ≥1 unit improvement from baseline on a scale of 0–10 in ≥3 of the following four domains (with no deterioration in the remaining domain): patient global assessment; pain assessment, function (BASDAI); and inflammation (questions 5 and 6 of BASDAI); ASAS40: improvement of ≥40% and ≥2 units improvement from baseline on a scale of 0–10 in ≥3 of the four domains (with no deterioration in the remaining domain); ASDAS: AS Disease Activity Score; BID: twice daily; FILG: filgotinib; IR: inadequate responder; JAK: Janus kinase; TOFA: tofacitinib; UPA: upadacitinib.

minimal or no activity against JAK1, JAK2 and JAK3 [106, 107]. A number of additional JAK/TYK inhibitors are currently in early development, but no clinical data have been published to date.

Importantly, some analyses do not show the relative selectivity of different JAK inhibitors, and results may vary depending on the assay that is used [83, 108]. In addition, the assays may not reflect the physiological concentrations and effects of JAK inhibitors in humans [108, 109]. Besides their selectivity profile, several notable further differences exist between JAK inhibitors, such as chemical structure, inhibition potencies, metabolism and excretion profiles. These variables indicate that the clinical profiles of JAK inhibitors are likely to have meaningful clinical differences.

Biomarker studies *in vivo* may inform precise and relevant *in vivo* effects. In keeping with the mode of action of JAK inhibitors, biomarker analyses have shown that UPA 15 mg once daily exerts broad direct inhibitory activity on multiple JAK1-dependent (IFN-α/β, IFN-γ, IL-6, IL-2, IL-5 and IL-7) pathways, indirectly on several JAK1-independent (IL-1, IL-23, IL-17, IL-18 and TNF) pathways, and other JAK-dependent cytokines such as GM-CSF [83] resulting in the inhibition of key functional pathways, such as leucocyte activation and mobility, inflammatory response and damage to connective tissue (Figs 1 and 2) [110]. Filgotinib has also been shown to reduce circulating proinflammatory cytokines and chemokines, adhesion molecules and markers of matrix remodelling associated with PsA [111] and AS [112]. In addition, preclinical models have demonstrated the beneficial impact of JAK–STAT blockade on the manifestations of SpA [113, 114] including via a TNF-independent mechanism [113]. These studies provided further evidence that JAK inhibition of multiple cytokines is a viable treatment approach in SpA and supported the initiation of several large-scale clinical trial programmes of JAK inhibitors in SpA.

JAK inhibitors in SpA: Efficacy

Three JAK inhibitors, tofacitinib, filgotinib and UPA, have been evaluated in patients with AS (Table 1) [16–18, 99]. Each of these studies was performed in patients with an inadequate response/intolerance to NSAIDs and evaluated one dose of the active treatment *vs* placebo for 12–16 weeks. All studies achieved their primary endpoints as well as key secondary endpoints, which included clinical outcomes such as ASAS20, ASAS40 and BASDAI50 responses as well as improvement in quality of life and reduction of inflammation on magnetic resonance imaging [16–18, 99]. Further studies of JAK inhibitors in axial SpA are ongoing, including a phase 3 programme of UPA in axial SpA (NCT04169373; SELECT-AXIS 2), which studies patients with AS with inadequate response to prior bDMARD therapy as well as patients with non-radiographic axial SpA. The efficacy and safety of SHR0302 (a JAK1 inhibitor) are also being evaluated in patients with AS in a phase 2/3 study (NCT04481139).

Several JAK inhibitors have been evaluated for the treatment of PsA including tofacitinib, UPA and filgotinib. Tofacitinib has been assessed in two phase 3 studies, OPAL Broaden [19] and OPAL Beyond [20] (Table 2). OPAL Broaden and OPAL Beyond enrolled patients with an inadequate response to conventional synthetic DMARDs (csDMARDs) and TNF inhibitors, respectively, and OPAL Broaden also included an active comparator

Table 2 Summary of key trials of JAK inhibitors in development in PsA

	Upadacitinib		Tofacitinib		Filgotinib	Deucravacitinib [103]
	SELECT-PsA 1 [101]	SELECT-PsA 2 [15]	OPAL Broaden [19]	OPAL Beyond [20]	EQUATOR [102]	
Phase	3	3	3	3	2	2
Population	Non-bDMARD-IR	bDMARD-IR	csDMARD-IR	TNF-IR	csDMARD-IR	csDMARD-IR, including TNF-IR
Treatment arms	UPA 15 mg QD UPA 30 mg QD ADA 40 mg EOW Placebo	UPA 15 mg QD UPA 30 mg QD Placebo	TOFA 5 mg BID TOFA 10 mg BID ADA 40 mg EOW Placebo	TOFA 5 mg BID TOFA 10 mg BID Placebo	FILG 200 mg QD Placebo	DEUC 6 mg QD DEUC 12 mg QD Placebo
Study duration	24 weeks	24 weeks	12 months	6 months	16 weeks	16 weeks
Number of patients randomized	1705	641	422	395	131	203
Primary endpoint/s	ACR20 at week 12	ACR20 at week 12	ACR20 at 3 months/ ΔHAQ-DI at 3 months	ACR20 at 3 months/ ΔHAQ-DI at 3 months	ACR20 at week 16	ACR20 at week 16
Results from primary endpoint	UPA 15 and 30 mg *vs* placebo: 71% and 79% *vs* 36%, $P < 0.001$ (both doses); ADA: 65%	UPA 15 and 30 mg *vs* placebo: 57% and 64% *vs* 24%, $P < 0.001$ (both doses)	ACR20: TOFA 5 and 10 mg *vs* placebo: 50% ($P = 0.01$) and 61% ($P < 0.001$) *vs* 33%; ADA: 52% ΔHAQ-DI: TOFA 5 and 10 mg *vs* placebo: –0.35 ($P = 0.006$) and –0.40 ($P < 0.001$) *vs* –0.18; ADA: –0.38	ACR20: TOFA 5 and 10 mg *vs* placebo: 50% and 47% *vs* 24%, $P < 0.001$ (both doses) ΔHAQ-DI: TOFA 5 and 10 mg *vs* placebo: –0.39 and –0.35 *vs* –0.14, $P < 0.001$ (both doses)	FILG *vs* placebo: 80% *vs* 33%, $P < 0.0001$	DEUC 6 and 12 mg *vs* placebo: 53% ($P = 0.0134$) and 63% ($P = 0.0004$) *vs* 32%

ACR20: ACR 20% improvement; ADA: adalimumab; bDMARD: biologic DMARD; BID: twice daily; csDMARD: conventional synthetic DMARD; DEUC: deucravacitinib; EOW: every other week; FILG: filgotinib; HAQ-DI: HAQ-Disability Index; IR: inadequate responder; QD: once daily; TOFA: tofacitinib; UPA: upadacitinib.

arm of adalimumab (ADA) 40 mg every other week (although it was not powered to assess superiority or non-inferiority of tofacitinib *vs* ADA). Both studies met their primary endpoints (American College of Rheumatology 20% improvement [ACR20] for OPAL Beyond and both ACR20 and change in Health Assessment Questionnaire-Disability Index for OPAL Broaden) with improvements also observed in several key PsA domains such as psoriasis, enthesitis and dactylitis [19, 20].

UPA has been assessed in two phase 3 trials in patients with PsA: SELECT-PsA 1 in patients with an inadequate response to non-biologic DMARDs [101] and SELECT-PsA 2 in patients with an inadequate response to bDMARDs [15] (Table 2). SELECT-PsA 1 included an ADA active comparator arm, with non-inferiority and superiority of UPA *vs* ADA included as ranked endpoints. Both trials met their primary endpoints (ACR20 at week 12) as well as showing improvements in psoriasis, dactylitis, enthesitis and quality of life endpoints. In SELECT-PsA 1, UPA inhibited radiographic progression (as assessed by Modified PsA Sharp/van der Heijde Score) *vs* placebo at week 24. Notably, both UPA doses were shown to be non-inferior to ADA for ACR20 response at week 12 in SELECT-PsA 1, and the UPA 30 mg dose demonstrated superiority.

Filgotinib has been assessed in a phase 2 study in patients with PsA and an inadequate response/intolerance to csDMARDs [102]. The study met its primary endpoint of ACR20 at week 16, and significant improvements were observed in signs and symptoms of PsA, including peripheral arthritis, psoriasis, enthesitis and patient-reported outcomes. Two phase 3 trials of filgotinib in PsA (PENGUIN 1 [NCT04115748] and PENGUIN 2 [NCT04115839]) have been terminated due to toxicity concerns.

Finally, deucravacitinib was assessed in a 16-week phase 2 trial in patients with PsA who had an inadequate response to $\geq$1 non-steroidal anti-inflammatory drug, corticosteroid and/or csDMARD [100]. The study met its primary endpoint of a dose–response relationship with deucravacitinib 6 mg and 12 mg for ACR20, and improvement in key secondary endpoints such as quality of life measures and enthesitis. This agent has also demonstrated efficacy in the treatment of psoriasis in a phase 3 trial, consistent with a mechanism of action involving TYK2 pathway inhibition, including IL-23-mediated signalling [100].

JAK inhibitors in SpA: Safety

As described above, JAK inhibitors block signalling initiated by multiple cytokines that mediate a variety of biological effects. Across the studies of JAK inhibitors in patients with AS and PsA, no new safety risks were identified with UPA, tofacitinib or filgotinib, with safety data consistent with the respective phase 3 RA studies [115–124]. Cross-indication safety overview of various agents in patients with RA, AS and PsA have consistently shown numerically lower rates of safety events among patients with PsA and AS, compared with that among patients with RA [125–127]. It has been proposed that this apparently lower rate may be a result of fundamental differences between patient cohorts; for example, patients with SpA are typically younger and have fewer comorbidities than patients with RA, and patients with AS typically require less immunosuppressant therapy than patients with RA [128, 129].

Adverse events of interest in patients receiving JAK inhibitors include infections (particularly herpes zoster), venous thromboembolism and laboratory abnormalities [130–133]. Similar to studies in RA, cases of herpes zoster have been observed in patients with SpA treated with JAK inhibitors, although the majority were non-serious and involved a single dermatome [15, 20, 101]. A small number of venous thromboembolism cases have also been observed in patients with SpA receiving JAK inhibitors [15, 101].

Finally, it should be noted that long-term safety data of JAK inhibitors in SpA are currently lacking, and therefore only limited safety conclusions can be drawn for events with longer latency or rare events based on the relatively short placebo-controlled periods of the clinical trials. However, longer-term open-label extension studies of JAK inhibitors in SpA are ongoing and should provide further clarity on this issue, particularly in patients with comorbidities that are common in SpA, such as type 2 diabetes, hypertension and dyslipidaemia.

Conclusions

The pathogenesis of SpA is complex and, although not fully understood, is thought to involve both environmental and genetic factors that together elicit a chronic inflammatory response involving the innate and adaptive immune systems. Several cytokines that have been implicated in the pathogenesis of SpA signal via the JAK–STAT pathway, supporting rational therapeutic intervention with JAK inhibitors. Although some bDMARDs have demonstrated efficacy through the blockade of individual cytokines, JAK inhibition may provide a more robust effect by blocking multiple cytokines and their downstream effects. Clinical trials of JAK inhibitors in patients with AS and PsA have shown improvements across multiple clinical domains of SpA (i.e. axial, peripheral, enthesitis, psoriasis) with an acceptable safety profile consistent with that observed in other indications such as RA. JAK inhibitors are therefore likely to become an important part of the overall treatment paradigm for SpA.

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Data availability statement

The data underlying this article are sourced from the public domain and are available in the articles cited throughout.

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