Review

Peripheral arthritis in psoriatic arthritis: from immunopathogenesis to therapy with Janus kinase inhibitors

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ABSTRACT

Psoriatic arthritis (PsA) is a chronic systemic inflammatory disease characterised by high phenotypic heterogeneity. Peripheral polyarticular, pauciarticular, axial, enthesitic, and dactylitic forms have been classically described, although it is not clear whether they all have the same pathophysiological mechanisms. Use of cytokine-targeted therapies in the last 20 years has significantly impacted the quality of life of patients with PsA even though a significant proportion of patients, regardless of the mechanism of action considered, remain non-responders, suggesting the need for better understanding of the pathophysiological basis of the disease to appropriately stratify patients and identify new therapeutic targets. The pre-clinical demonstration of the pathophysiological relevance of the JAK/STAT pathway in the pathogenesis of PsA and the emerging efficacy data from randomised controlled trials of JAK inhibitors in PsA patients have set the stage for a new pharmacological era in patients with PsA. In this review, we discuss the rationale for using approved JAK inhibitors for treatment of peripheral PsA and their positioning in the context of EULAR/GRAPPA guidelines.

Introduction

Psoriatic arthritis (PsA) is a chronic systemic inflammatory disease characterised by high phenotypic heterogeneity (1). Peripheral polyarticular, pauciarticular, axial, enthesitic, and dactylitic forms have been classically described, although it is not clear whether they all have the same pathophysiological mechanisms (1). A pathophysiological interpretation of the different subsets of PsA may include understanding the different cytokine pathways for each of the discrete clinical manifestations of the disease. At the same time, one can also imagine a common pathophysiological basis in which some pathways, such as that of type 3 immunity, might be predominantly involved in the presence of inflammation. Obviously, a third possibility linked to more stochastic behaviour of biological phenomena, that is indirectly observed, cannot be completely excluded. To date, however, it is not clear which of the three hypotheses is the most likely and, despite some initial attempts at precision medicine, the choice of the most appropriate drug for a specific patient with PsA still remains empirical.

Among the different clinical entities, peripheral joint involvement is the most common and potentially debilitating feature of PsA, being progressive in most patients with PsA (1). Clinical trials analysing the efficacy of drugs with different mechanisms of action on peripheral arthritis of patients with PsA have shown a comparable degree of efficacy regardless of the specific pathway affected (2, 3). To date, an ACR 50 response can be achieved in around 50–60% of patients (2, 3). The high number of non-responders or partially responders thus suggest the need to better understand the pathophysiological basis of the disease to appropriately stratify patients and identify new therapeutic targets. The advent of JAK inhibitors in the therapy of patients with PsA represents a significant innovation in this scenario. Based on these premises, in this review we will discuss the rationale for using approved JAK inhibitors in the treatment of peripheral PsA and their positioning in the context of EULAR/GRAPPA guidelines.

Lessons from animal models

Animal models of PsA have reinforced the importance of the JAK/STAT path-

way in its pathogenesis. Several murine models have been used for this purpose, such as A20myelKO mice, SKG mice, and R26STAT3Cstopfl/fl CD4Cre mice. A20, also known as TNF-α-induced protein 3, is a crucial negative regulator of nuclear factor-κB (NF-κB)-dependent inflammation (4). Single nucleotide polymorphisms in A20 have been associated with several immune-mediated inflammatory diseases, including rheumatoid arthritis, systemic lupus erythematosus, and psoriasis (4, 5) with cell-specific deletion of A20 resulting in diverse inflammatory phenotypes (6-9). In the study by De Wilde *et al*., inflammation was assessed in a time-dependent manner showing that enthesitis is an early inflammatory lesion in A20myelKO mice, preceding joint inflammation (10). Interestingly, A20 negatively modulated signal transducer and activator of transcription-dependent gene transcription in myeloid cells in both unstimulated conditions and after stimulation with interferon-γ (mainly phosphorylating STAT1) or interleukin-6 (strongly phosphorylating STAT3). The increase in STAT1 gene transcription in the absence of A20 was shown to be JAK-STAT-dependent since a marked reduction in STAT1 gene transcription was seen after treatment of A20-/- myeloid cells with tofacitinib. To confirm an *in vivo* link between A20 and JAK-STAT signalling in the pathogenesis of enthesitis in A20myelKO mice, the authors treated mice with tofacitinib citrate, dosed orally at 50 mg/kg twice a day, or with a placebo control, and evaluated clinical development of disease. A clear reduction in the clinical and histopathological scores was observed in tofacitinib citrate-treated mice, thus confirming the role of the JAK-STAT pathway in the development of enthesitis *in vivo* (10). In addition, *in vivo* tofacitinib treatment reduced the transcription of STAT1 and STAT1-dependent genes, such as CXCL10 and MX1, in myeloid cells isolated from $A20^{myelKO}$ mice.

The SKG mouse harbours a point mutation in the ZAP-70 gene which gives rise to reduced T-cell receptor (TCR) signalling and multi-organ inflammation under microbial influence, mimicking elements of the pathogenesis of spondyloarthritis (SpA) in humans (11). Nishimura *et al*. evaluated the effects of the JAK inhibitor tofacitinib in SKG mice on myeloid-derived suppressor cells (MDSCs), a heterogeneous population of cells that can suppress T cell responses (12). In that study, the authors demonstrated that the numbers of MDSCs and polymorphonuclear MDSCs (PMN-MDSCs) were significantly increased in the spleens of SKG mice following induction of arthritis. Adoptive transfer of MDSCs to recipient arthritic mice reduced the severity of arthritis and treatment with tofacitinib ameliorated the progression of arthritis in SKG mice by inducing a significantly higher numbers of MDSCs and PMN-MDSCs in the bone marrow of these animals, facilitating the differentiation of bone marrow cells to MDSCs, and inhibiting their differentiation to dendritic cells.

Recently, Yang *et al*. characterised a novel murine model of Th17-driven cutaneous and synovio-entheseal disease directed by T cell-specific expression of a hyperactive STAT3 allele (13). In particular, $R26STAT3C^{stopfl/fl}$ CD4Cre mice were crossed onto an IL-22 knockout background and the contribution of Th17 cytokines in the pathogenesis of PsA was evaluated. $R26STAT3C^{stopfl/fl}$ CD4Cre mice developed acanthosis, hyperkeratosis, and parakeratosis of the skin, as well as enthesitis/tendonitis and peri-articular bone erosion in different joints that highly resemble PsA. T cell specific expression of a hyperactive STAT3C allele induced an augmented Th17 response in these animals. Careful characterisation revealed an increase in osteoclast progenitor cells (OCP) and RANKL producing cells. Abrogation of Th17 cytokines, IL-17, or IL-22 improved both skin and bone phenotypes in $R26STAT3C^{stopfl/fl}$ CD4Cre mice, revealing a central role of Th17 cells in the regulation of OCP numbers and RANKL expression on stromal cells.

The effect of JAK inhibition on an SKG mouse model has been also studied by Maeda *et al*. (14). In that study, JAK inhibitors significantly decreased clinical and histologic inflammation scores with 50% inhibition of periosteal/entheseal bone formation at peripheral sites. Global gene expression analysis of inflamed tissue from entheses identified distinct gene expression patterns at sites of bone formation and sites of inflammation without bone formation. Differentially regulated genes included cartilage and bone markers, such as biglycan and collagen type I alpha 1, with significant enrichment of major skeletal pathway regulators at sites of periosteal bone formation, including TGF-beta, Wnt3A, and the aryl hydrocarbon receptor, which are all implicated in osteoclastogenesis.

TYK2, also belonging to the JAK family, might also contribute to PsA pathogenesis since TYK2 single-nucleotide polymorphisms (SNPs) have been associated with PsA susceptibility (15). TYK2 has been demonstrated to mediate signalling through the type 1 IFN receptor (IFNAR), IL-10 family receptors (IL-10R and IL-22R), and IL-12 family receptors (IL-12R and IL-23R) (16). TYK2 deficiency in humans induces increased sensitivity to mycobacterial and viral infections (17), while TYK2-deficient mice are protected from Th17-mediated autoimmune disease (18, 19). Gracey *et al*. have recently shown that TYK2 inhibition in murine models of SpA has a protective effect associated with inhibition of type 3 immunity (20). In that study, the authors characterised a potentially novel small-molecule inhibitor of TYK2 (NDI-031407, an enzymatic inhibitor of Tyk2 that differs from other novel allosteric inhibitors (21)) that blocked IL-23 signalling *in vitro* and inhibited disease progression in animal models of SpA. Using TYK2-inactive mice, the authors demonstrated that modulation of IL-17 and IL-22 by IL-23 depends on different JAK/STAT signaling since IL-22 production followed TYK2/JAK2/STAT3 activation, while IL-17A was mainly dependent on JAK2. All these studies point to the important role of the JAK/STAT pathway in the pathogenesis of preclinical models of PsA, thus setting the stage for a rationale for their use in PsA.

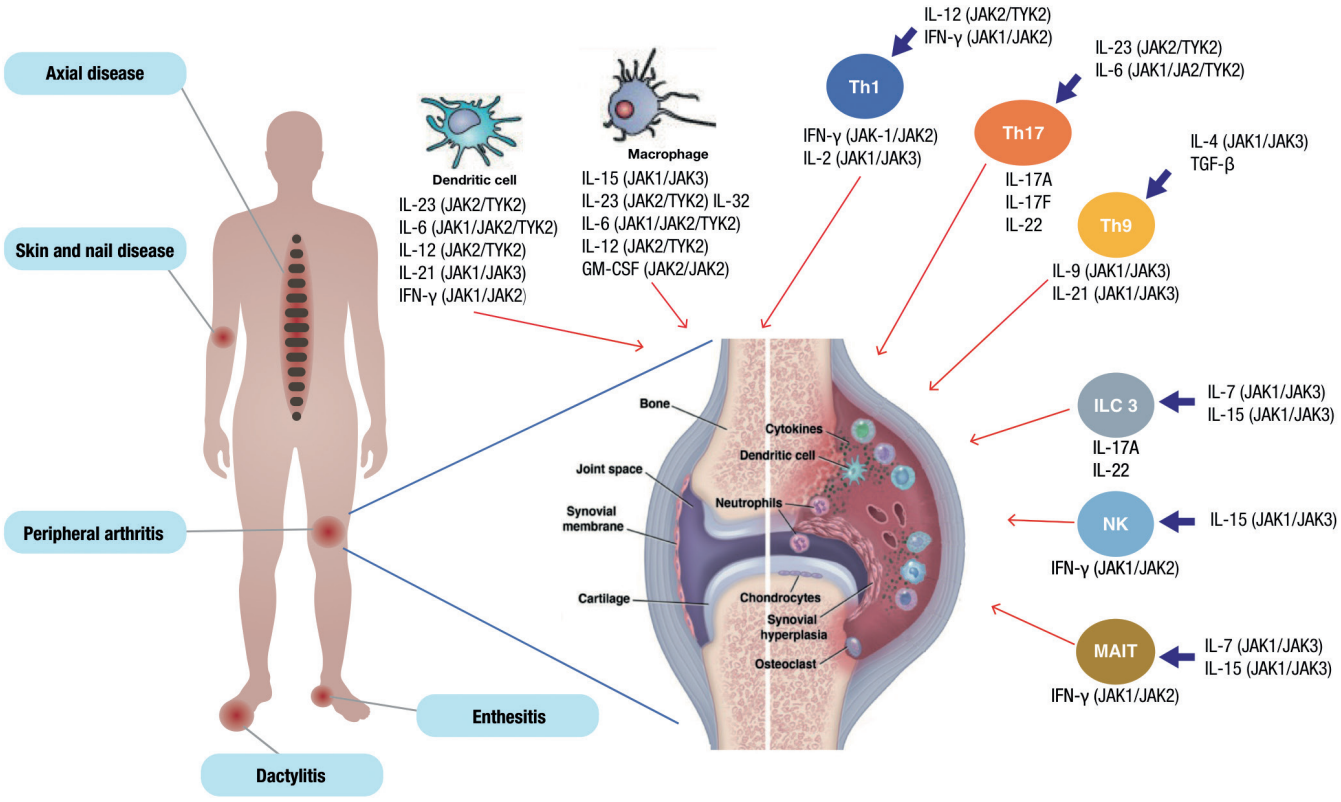

Fig. 1. Summary of key cell types and secretion of key inflammatory mediators in peripheral psoriatic arthritis. Dendritic cells and macrophages, as well as innate lymphoid cells, mucosal-associated invariant T cells, and natural killer cells mostly secrete proinflammatory cytokines as shown. In addition, Th1, Th9, and 17 T-cells secrete both proinflammatory and anti-inflammatory cytokines. All these proinflammatory mediators have the ability to activate synovial neutrophils, chondrocytes, and osteoclasts, which in turn secrete proinflammatory molecules that recruit additional immune cells into joints, which creates an enduring inflammatory response. The inflamed synovial microenvironment leads to the formation of the synovial pannus, entheseal inflammation, and joint destruction.
Th: T-helper cell. ILC: innate lymphoid cell; MAIT: mucosal-associated invariant T; NK: natural killer; Th: T-helper cell; TNFα: tumour necrosis factor α; IFNγ: interferon γ.; L: interleukin; JAK: Janus kinase.

Role of JAK/STAT pathway in the pathophysiology of PsA synovitis

PsA synovium is the result of the abnormal interaction of many proinflammatory cytokines and growth factors, which contribute to the recruitment of inflammatory cells from the bloodstream to the underlying tissue (22). Type 3 immunity, with cytokines such as IL-23 and IL-17, has been shown to be primarily involved in the pathogenesis of synovitis in PsA (23), although the expression of other cytokines such as tumour necrosis factor alpha (TNF-alpha), IL-1b, IL-6, and IL-18 is increased in PsA synovitis (24). Recent data also suggest that the impaired balance between IL-36 agonists-antagonists and Th9 activation may drive inflammation in PsA (25-29). All these studies, far from identifying a hierarchical axis more involved in the pathogenesis of PsA synovitis, support the idea that multiple cytokine pathways, possibly simultaneously, can contribute to the pathogenesis of PsA synovitis. Many of the aforementioned cytokines signal through pairs of the JAK family of receptor-associated tyrosine kinases such as IL-23 (JAK2/TYK2) (30), IL-6 (JAK1/JAK2) (31) and IL-9 (JAK1/JAK3) (32) (Fig. 1). The activated JAKs in turn activate STAT, which ultimately drive gene transcription. A recent study investigated the therapeutic potential of several JAK inhibitors on mononuclear cells derived from patients with SpA and healthy controls cultured *in vitro* under Th17-promoting conditions (33). The levels of IL-17A, IL-17F, IL-22, GM-CSF, and IFN-γ were assessed by ELISA and inhibitory effects were studied with Phosphoflow. siRNA-mediated silencing of JAK1/2/3 and TYK2 in $CD4^+$ T cells led to inhibition of IL-17A, IL-17F and IL-22 as evaluated by ELISA, Western Blot, qPCR, and Phosphoflow. Moreover, an important *in vitro* inhibitory effect of several JAK inhibitors with different specificities, tofacitinib, baricitinib, ruxolitinib, and CEP-33779 was demonstrated on the production of IL-17A, IL-17F, and IL-22 by $TCD4^+$ lymphocytes. A similar effect was obtained by silencing JAK1-3 and TYK2 without affecting cell viability or proliferation. This suggests that some JAK inhibitors can inhibit multiple Th17 cytokines simultaneously and that improved targeting of TYK2 or other JAK isoforms has the potential to confer tailored effects on Th17 responses.

In support of the important pathogenetic role of JAK/STAT in PsA synovitis, over-expression of STAT1 and STAT3 was documented by Gao *et al.* in the synovium of patients with PsA compared to osteoarthritis (34). In the same study, it was demonstrated that tofacitinib significantly decreased the

expression of pSTAT3, pSTAT1, and NFκBp65 and induced SOCS3 and PIAS3 expression in PsA synovial fibroblasts PsA-FLS and synovial explant cultures. Functionally, PsA-FLS invasion, network formation, and migration were inhibited by tofacitinib together with a significant reduction in the secretion of IL-6, IL-8, MCP-1, MMP9/MMP2, and MMP3. Increased levels of JAK1, STAT3, and STAT1 phosphoproteins have been observed by Fiocco *et al*. in isolated T cells from the synovial fluid of PsA patients, accompanied by the synovial, but not peripheral blood, expansion of T CD4(+) IL-17A-F(+) cells, as well as T CD4(+) cells expressing IL-23Rp19 (T CD4(+) IL-23R(+)) (35). A further confirmation that targeting JAK-STAT signalling may alter PsA synovial fibroblast pro-Inflammatory and metabolic function derives from a recently published study in which O'Brien *et al*. isolated and cultured primary PsA-FLS with different JAK inhibitors such as peficitinib, filgotinib, baricitinib, or upadacitinib, in the presence of oncostatin M (OSM) (36). OSM induces pSTAT3 expression in PsA-FLS and the secretion of MCP-1 and IL-6 was inhibited by all JAK inhibitors. PsA-FLS cell invasion, migratory capacity, and MMP1, MMP3, and MMP9 were also suppressed following treatment with a JAK inhibitor. These functional effects were also accompanied by a change in the cellular bioenergetic profile of PsA-FLS, where JAK inhibition significantly decreased glycolysis and oxidative phosphorylation, resulting in a shift to a more quiescent phenotype.

Raychaudhuri *et al*. have shown that generation of pathological $CD4^{+}CD11a^{+}$CD45RO+IL-17+ T cells and their proliferation are regulated by the JAK-STAT signalling system (37). In both PsA and controls, sorted activated CD3+ T cells responded to IL-23 by activating JAK2 and STAT3, whose phosphorylation is markedly inhibited by tofacitinib. Fluorescence-activated cell sorting analyses of activated CD3+T cells in patients with PsA demonstrated that IL-23 induced marked upregulation of IL-17 in memory T cells (CD11a+CD45RO+) and the expansion of activated memory CD4+IL-17+ T cells, the proliferation of which was significantly reduced by incubation with tofacitinib. The effect of tofacitinib in modulating expansion of inflammatory IL-17-producing cells might be related to a direct effect on CD4+ T cells and the ability of tofacitinib to modulate maturation of human monocyte-derived dendritic cells (DCs) induced by lipopolysaccharide (LPS) stimulation (38). Tofacitinib treatment of CD4+ T cells isolated from synovium and peripheral blood has been shown to inhibit the production of IL-17 and IFN-γ in a dose-dependent manner, affecting both proliferation and transcription (39). In addition, tofacitinib has been demonstrated to decrease the expression of CD80/CD86 and the production of TNF, IL-6, and IL-1β in a concentration-dependent manner in LPS-stimulated DCs (40). Furthermore, tofacitinib suppressed production of type I IFN and activation of interferon regulatory factor (IRF)-7 and decreased the T cell stimulatory capability of DCs (38). More recently, Russel *et al*. evaluated whether JAK inhibition with tofacitinib may modulate the key SpA associated cytokines, TNF, and IL-17A in entheseal-derived human cells. In this study, IL-17A and TNF cytokine production from both entheseal CD4+ T-cells and CD8+ T-cells was effectively inhibited by tofacitinib (41).

A further confirmation of the pathophysiological relevance of JAK/STAT signalling in PsA derives by the study by Macaubas *et al*. in which high dimensional mass cytometry (CyTOF) was used to analyse the levels of phosphorylated STAT3 (pSTAT3) in circulating immune cell subpopulations from active and inactive PsA patients (42). In particular, the frequency of 16 immune cell populations and the levels of the activated forms of STAT3 (pSTAT3), STAT1 (pSTAT1) and Src (pSrc) in whole blood from patients with PsA were evaluated. Increased levels of pSTAT3 were found in all CD4+ T cell subsets analysed, specifically, Th1, Th2, Th17, T follicular helper (Tfh), and T regulatory (Treg) as well as in $CD14^{+}$CD16- (classical) monocytes from patients with active PsA.

JAK inhibition in the management of PsA

The studies discussed above underline the complex distribution and the pleiotropic role of JAK/STAT proteins in different cell types and possibility that their modulation might therefore represent a potential therapeutic target in PsA (43). Based on these premises, several randomised clinical trials (RCT) have been performed to evaluate the efficacy and safety of JAK inhibitors in patients with PsA. The Phase 2 and 3 studies with JAK inhibitors in PsA are summarised in Table I. Tofacitinib was studied in the OPAL trials (44, 45), upadacitinib in the SELECT-PsA trials (46, 47), and filgotinib in the Phase 2 EQUATOR study (48). A clinically significant benefit of JAK inhibitors was seen in most outcomes. A meta-analysis of these 5 trials reported that ACR20 response rates were significantly higher in patients receiving a JAK inhibitor compared to placebo (OR 3.78, 95% CI 2.72–5.24) as well as significant improvement in enthesitis, dactylitis, PASI75, and quality of life (49).

Regarding safety aspects, since approval of tofacitinib for rheumatoid arthritis in 2012, specific safety concerns associated with JAK inhibitors have emerged, namely reactivation of herpes zoster and serious infections (50-52). More recently, additional safety considerations include malignancies, venous thromboembolic events (VTE) and major adverse cardiovascular events (MACE), based on data from the ORAL Surveillance study (53). ORAL Surveillance was a large, post-approval, open-label, safety event-driven clinical trial in patients with moderate to severe rheumatoid arthritis despite methotrexate treatment. In all, 1455 patients received tofacitinib 5 mg BID, 1456 tofacitinib 10 mg BID, and 1451 received a TNF inhibitor. It was reported that the incidences of co-primary endpoints MACE and malignancies, excluding non-melanoma skin cancer, were higher with the combined tofacitinib doses (3.4% [n=98] and 4.2% [n=122], respectively), than with a TNF inhibitor (2.5% [n=37] and 2.9% [n=42], respectively). In addi-

Table I. Phase 2 and 3 studies on JAK inhibitors for treatment of PsA.

Jak inhibitor	Author, year	Phase Study name	Study population	Duration	Primary endpoint(s)	Main outcomes
Tofacitinib	Mease, 2017 (45)	Phase 3 OPAL BROADEN	422 patients randomised to: tofacitinib 5 mg BID (n=107), tofacitinib at a 10 mg BID (n=104), adalimumab 40 mg dose administered subcutaneously once every 2 weeks (n=106), placebo with a blinded switch to 5 mg tofacitinib at 3 months (n=52), or placebo with a blinded switch to 10 mg tofacitinib dose at 3 months (n=53).	12 months	Percentage patients with ACR20 response at 3 months Change from baseline on the HAQ-DI scores at 3 months	ACR20 response rates at month 3 were 50% for 5 mg tofacitinib and 61% for 10 mg tofacitinib group *vs*. 33% with placebo (p=0.01 for the comparison of the 5-mg dose with placebo; p<0.001 for the comparison of the 10-mg dose with placebo); the rate was 52% in the adalimumab group. The mean change in HAQ-DI score was -0.35 for 5 mg tofacitinib group and -0.40 for 10 mg tofacitinib *vs*. -0.18 for placebo (p=0.006 for the comparison of 5 mg with placebo; p<0.001 for comparison of 10 mg with placebo); the score change was -0.38 in the adalimumab group
Tofacitinib	Gladman, 2017 (44)	Phase 3 OPAL BEYOND	395 patients randomised to four regimens: 5 mg tofacitinib BID (n=132); 10 mg tofacitinib BID (n=132); placebo, with a switch to 5 mg tofacitinib BID at 3 months (n=66); or placebo, with a switch to 10 mg tofacitinib BID at 3 months (n=65)	6 months	Percentage patients with ACR20 response at 3 months Change from baseline on the HAQ-DI scores at 3 months	At 3 months, rates of ACR20 response were 50% with the 5-mg dose of tofacitinib and 47% with the 10-mg dose, compared with 24% with placebo (p<0.001 for both comparisons); the corresponding mean changes from baseline in HAQ-DI score were -0.39 and -0.35, compared with -0.14 (p<0.001 for both comparisons).
Upadacitinib	McInnes, 2021 (46)	Phase 3 SELECT-PsA 1	1704 patients randomised 1:1:1:1 ratio to receive upadacitinib of 15 mg or 30 mg once daily, placebo, or subcutaneous adalimumab (40 mg every other week)	24 weeks	ACR20 response at week 12	ACR20 response at week 12 was 70.6% with 15-mg upadacitinib, 78.5% with 30-mg upadacitinib, 36.2% with placebo (p<0.001 for both upadacitinib doses *vs*. placebo), and 65.0% with adalimumab
Upadacitinib	Mease, 2021 (47)	Phase 3 SELECT-PsA 2	642 patients randomised to oral upadacitinib 15 or 30 mg once daily, or placebo switched to upadacitinib 15 or 30 mg once daily at week 24	6 months	ACR20 response at week 12	At 3 months ACR20 response was achieved in 56.9% receiving upadacitinib 15 mg, 63.8% upadacitinib 30, and 24.1% for placebo (p<0.001 for both upadacitinib doses *vs*. placebo
Filgotinib	Mease, 2018 (48)	Phase 2 EQUATOR	131 patients randomised to filgotinib (n=65) or placebo (n=66)	16 weeks	ACR20 response at week 16	80% of patients with filgotinib and 33% of those on placebo achieved ACR20 at week 16 (p<0.0001)

HAQ-DI: Health Assessment Questionnaire-Disability Index.

tion, a safety alert for higher VTE and mortality was generated during the study for the tofacitinib dose of 10 mg BID (53).

Randomised clinical trials (RCTs) have thus confirmed that blocking the JAK/STAT pathway is clinically relevant in patients with PsA. Moreover, these RCTs led to the regulatory approval of JAK inhibitors as therapy for PsA (54) and inclusion of JAK inhibitors in the EULAR and GRAPPA guidelines for the treatment of PsA (55, 56). A systematic review of tofacitinib in PsA indicated that tofacitinib may have similar efficacy to the TNF inhibitor (TNFi) adalimumab for joint involvement, but lower efficacy in skin psoriasis (49). Satisfactory efficacy of tofacitinib is also observed in populations that respond poorly to TNF inhibitors (45). Similar results were obtained in PsA in an RCT comparing upadacitinib to placebo in patients naive to bDMARDs or bio-experienced (47). RCT on filgotinib, another JAK1 selective inhibitor, in PsA also showed promising efficacy in a phase II study (57).

Recently, the EULAR updated its recommendations for PsA based on a systematic review of the literature identifying a patient-specific phenotype and specific place in therapy for JAK inhibitors (56). The recommendations emphasise how that inhibition is an appropriate therapeutic option for treatment of patients with polyarthritis or mono/oligoarthritis who have failed treatment with at least one csDMARD and at least one bDMARD - or when a bDMARD is inappropriate. In this case, inappropriate means, for example, non-adherence to injections or a strong patient preference for an oral drug in accordance with the general principles of shared decision making. However, the EULAR panel agreed that a phased approach would normally be a csDMARD followed by a bDMARD, and subsequently another bDMARD or JAK inhibitor.

The GRAPPA guidelines for PsA have also been recently updated and published (55). Among the new recom-

mendations, the use of JAK inhibitors is strongly recommended in PsA patients with peripheral arthritis who are csDMARD naive and those with inadequate response to a csDMARD or b-DMARDs experienced.

Conclusions

The involvement of the JAK/STAT pathway in the pathogenesis of peripheral arthritis in patients with PsA appears to be strongly supported by the literature data herein discussed. The introduction of therapy with JAK inhibitors in the treatment of patients with PsA in the EULAR and GRAPPA guidelines acknowledges the importance of blocking this pathway, as supported by data from RCTs. We are obviously far from defining a hierarchy between different JAKs in the synovitis of patients with PsA, but the introduction of JAK inhibitors in the therapeutic armamentarium undoubtedly represents a fundamental advance in the management of patients with PsA. More precise targeting of TYK2 or other JAK isoforms is a step in this direction in conferring specific effects on Th17 responses. The correct temporal place in therapy of a JAK inhibitor, whether in the early stage of the disease (with the difficulty of defining a true early stage) or after therapies aimed at blocking specific cytokines, remains to be defined. In addition, greater use of personalised medicine in PsA has been advocated (58). In this regard, studies specifically investigating head-to-head comparisons with bDMARDs and in patients with early PsA could help to further define these aspects in the near future.

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