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JAK1 selective inhibitors for the treatment of spondyloarthropathies

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Abstract

As our understanding of the pathogenesis of SpA improves, focus has turned to the role janus kinase (JAK)-mediated signal transduction and inhibiting its actions as a therapeutic mechanism. Small molecule inhibitors of JAK exist, with variable selectivity for the different JAK isoforms. Less selective JAK inhibitors have variable efficacy and safety profiles, prompting the investigation of selective JAK1 inhibition. In this review, we summarize the current phase 2 and 3 clinical trial data, evaluating the use of JAK1 selective inhibitors in the treatment of SpA, particularly AS and PsA. Selective JAK1 inhibition offers a promising therapeutic approach, however further longer-term trials are needed to fully establish their efficacy and safety at higher doses, and their use in the greater continuum of SpA.

Key words: spondyloarthropathies, selective janus kinase inhibitors, psoriatic arthritis, ankylosing spondylitis, treatment, axial spondyloarthritis, management

Rheumatology key messages

- Janus kinase is implicated in cytokines' signal transduction in the pathogenesis of SpA.
- Selective janus kinase 1 inhibition appears effective in PsA and AS with reasonable safety data.
- Selective janus kinase 1 inhibitors may show superior efficacy and safety compared with non-selective janus kinase inhibition.

Introduction

SpA are a heterogeneous group of inflammatory conditions, which include axial SpA (AxSpA), AS and PsA [1, 2]. AxSpA has two subsets: disease with radiographic sacroiliac joint changes (termed AS or radiographic AxSpA) and without [non-radiographic AxSpA (nr-AxSpA)] [1]. They are typified by inflammatory axial disease, peripheral arthritis, enthesitis and sacroiliitis, as well as a range of extra-articular associations, including psoriasform skin lesions, uveitis and IBD [1, 2].

The chronic inflammatory pathogenesis of SpA is complex and multifactorial, involving multiple pro-inflammatory cytokines many of which use signal transduction pathways, mediated by janus kinase (JAK) [2, 3]. This is a group of intracellular tyrosine kinase proteins, comprising four isoforms: JAK1, JAK2, JAK3 and tyrosine kinase 2 [2–4]. Therefore, targeting JAK inhibition offers potential for treatment of articular and extra-articular manifestations of SpA [2].

The appropriate treatment for SpA depends upon the subtype of disease, presenting symptoms, disease activity, other extra-articular disease involvement and comorbidities [2]. Typically, treatment trials have focused on predominant axial disease, including patients with AxSpA/AS, or predominantly peripheral disease, most commonly PsA. For AxSpA, current treatments are limited beyond NSAIDs [1, 2, 5]. Conventional synthetic DMARDs (csDMARDs) are not effective in axial disease and so for people unresponsive to NSAIDs, biological DMARDs (bDMARDs) are used [1, 2, 5]. To date, only two different second-line treatment mode of actions have been licensed, which are TNF inhibitors (TNFi) and mAbs against IL-17A [1, 5, 6].

The most recent national and international recommendations for the treatment of AxSpA [from Assessment of SpondyloArthritis international Society (ASAS) and

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EULAR in 2016] do not include JAK inhibitors (JAKi) due to limited evidence [7]. EULAR recommendations from 2020 consider the use of JAKi as a second-line option for the treatment of PsA, namely following the inadequate response to csDMARDS and bDMARDs, including TNFi, and inhibitors of IL-17A and IL-12/23 [8].

Evidence for therapies in PsA differs from that of AxSpA. Although evidence quality is poor, it is accepted that csDMARDs do show some efficacy in peripheral arthritis in PsA and for other extra-articular domains such as the skin. In peripheral disease, bDMARDs are commonly used after csDMARDs, with both TNFi and IL-17A inhibitors having approval in PsA. In addition to these therapies, there is also evidence of efficacy for the peripheral musculoskeletal system and approvals in PsA for additional targeted drugs, including ustekinumab (a p40 IL-12/23 inhibitor) and apremilast (a phosphodiesterase 4 inhibitor) [5].

However, there is a significant proportion of patients who either cannot tolerate existing therapies or experience inadequate responses to therapy [2, 8]. Even in patients with an initial response to therapy, it is clear that a significant proportion of patients may lose that response to treatment over time, requiring alternative therapies. Therefore, targeting different mechanisms of action offer potential to ameliorate the unmet need in SpA treatment [2].

The newest mode of treatment for SpA is JAKi [4]. The first available JAKi, tofacitinib, is a relatively non-selective JAKi that has a current licence for treatment of PsA. However, the selectivity for specific JAK isoforms is relative between drugs, and those currently in development mainly target JAK1 inhibition [3, 4]. This article will review the evidence of selective JAK1 inhibitors in SpA. Most data to date on selective JAKi focus on their use in AS and PsA, not nr-AxSpA.

Existing JAKi

Various JAKi are being investigated to evaluate their use in autoimmune disease [2]. Tofacitinib is an oral non-selective JAKi that has been investigated in SpA clinical trials [2, 9–12]. It is available and licensed for the treatment of PsA, however it is not currently approved for use in AS [2, 9–12]. Tofacitinib has shown preferential selectivity for JAK3 and/or JAK1 inhibition, over JAK2 [2, 10, 11].

Two phase 3 clinical trials have shown clinical efficacy of tofacitinib in PsA [9, 10]. These randomized-controlled trials include the Oral Psoriatic Arthritis Trial (OPAL) Broaden and OPAL Beyond [9, 10]. OPAL Broaden (NCT01877668) evaluated tofacitinib treatment in patients with active PsA, with previous inadequate responses to csDMARDs [9]. Treatment regimens of tofacitinib 5 mg twice daily (BD) and 10 mg BD offered improvements at 3 months, in ACR20 responses (20% improvement from baseline measures) and HAQ–Disability Index (HAQ-DI) scores, when compared with placebo [9]. Relative to baseline, this was maintained at 12 months [9]. OPAL Beyond (NCT01882439) evaluated tofacitinib treatment in patients with active PsA, in whom previous treatment with TNFi therapy was inadequate [10]. Tofacitinib treatment regimens of 5 mg BD and 10 mg BD showed significant improvements in ACR20 responses and HAQ-DI scores (compared with placebo) at month 3, and was maintained to month 6 (relative to baseline) [10]. Adverse effects observed in both trials were more frequent with tofacitinib compared with placebo, namely infection and transaminitis [9, 10]. In both of these studies, tofacitinib was prescribed alongside MTX and therefore the licence in PsA requires concomitant MTX therapy [9, 10].

A 16-week phase 2, dose-ranging trial (NCT01786668) compared the efficacy and safety of tofacitinib in patients with active AS, naïve to biologic therapy [11]. This involved tofacitinib treatment (2, 5 or 10 mg BD) for 12 weeks, followed by a 4-week 'washout', compared with placebo [11]. Significantly higher rates of improvement in the ASAS20 responses was seen with tofacitinib 5 mg BD (*vs* placebo) [11]. Tofacitinib 5 mg and 10 mg BD showed a dose-dependent improvement in objective disease measures, including change in baseline Spondyloarthritis Research Consortium of Canada (SPARCC) MRI scores of spine and sacroiliac joints at week 12 [11]. Greater improvement responses to tofacitinib were positively correlated in patients with greater baseline CRP and MRI inflammation [11].

Post hoc analysis of this trial evaluated the proportion of patients achieving 'minimally important change' in the SPARCC MRI scores, and if this correlated to clinically meaningful improvement [12]. It found 3-fold more patients achieving minimally important change with all doses of tofacitinib, in both sacroiliac and spine scores, compared with placebo [12]. It also concluded that around one in three patients treated with tofacitinib experienced clinically meaningful reduction in spinal inflammation at 12 weeks [12]. This indicates the benefits of tofacitinib to axial disease, however trials evaluating longer term follow-up are required to establish its full efficacy [11, 12].

Selective JAK1 inhibitors

Clinical trials exist evaluating selective JAK1 inhibitors in the treatment of SpA [13–17]. These include filgotinib and upadacitinib, in the treatment of AS and PsA; however, there are currently no trials investigating the efficacy of JAK1 inhibitors in nr-AxSpA [13–17].

Key trials in AS

TORTUGA (NCT03117270), a phase 2 trial, found filgotinib to be effective in AS, when compared with placebo [13]. Biologic-naïve patients with active AS, and previous inadequate responses or contraindications to at least two NSAIDs, received filgotinib 200 mg once daily (OD) orally for 12 weeks [13]. The use csDMARDs was allowed, requiring at least 12 weeks' use before

screening, on a stable dose for 4 weeks prior to baseline [13]. The treatment and placebo arms included 40% and 38% of patients using csDMARDs respectively [13]. The prior use of one TNFi was permitted (capped at 30% of patients enrolled), with variable washout periods for each type, before screening [13]. Treatment and placebo arms included 7% and 12% of these patients, respectively [13]. The primary outcome was the reduction in Ankylosing Spondylitis Disease Activity Score (ASDAS) at week 12 [13]. The study found that filgotinib significantly reduced disease activity from baseline scores by week 12 [13]. The mean changes from baseline were −1.47 (S.D. 1.04) with filgotinib and –0.57 (S.D. 0.82) with placebo, and least-squares mean difference (LSMD) of –0.85 (95% CI −1.17, −0.53; $P < 0.0001$) [13]. Decreased SPARCC MRI scores were seen with filgotinib (compared with placebo) for spine [−5.76 (S.D. 11.13) *vs* 0.52 (S.D. 7.47), respectively; $P = 0.0066$] and sacroiliac joints [−3.52 (S.D. 7.31) *vs* 0.06 (S.D. 3.51), respectively; $P = 0.0150$] [13].

Rapid therapeutic benefit from filgotinib was observed, with significant reduction in disease activity after week 1 and overall beneficial effect on peripheral disease symptoms [13]. Adverse events noted, in both treatment and placebo groups, most commonly included nasopharyngitis and infection [13]. One patient (with a heterozygous factor V Leiden mutation) in the treatment group developed a grade 2 calf deep vein thrombosis [13]. This was considered non-serious [13]. No venous thromboembolic events (VTE) were reported in the placebo arm [13]. No new safety concerns were raised [13]. Phase 3, longer-term investigation of oral filgotinib is required to establish its safety and efficacy in the treatment of active AS. Further research is needed to evaluate its use in the greater continuum of AxSpA, notably nr-AxSpA and patients with AxSpA who have previously received biologic therapies.

The efficacy of upadacitinib in AS was investigated in a phase 2/3 trial, SELECT-AXIS1 (NCT03178487), over 14 weeks [14]. Patients with active AS, and prior inadequate response or contraindication to two or more NSAIDs, were trialled on oral upadacitinib 15 mg OD [14]. Significantly more patients treated with upadacitinib (*vs* placebo) showed an ASAS40 response [52% *vs* 26% ($P = 0.0003$); 26% treatment difference (95% CI 13, 40)] [14]. Upadacitinib offered rapid benefit (earliest week 2) and significant improvement in multiple secondary endpoints pertaining to disease activity (BASDAI, ASDAS and ASAS partial remission), radiological inflammation (SPARCC MRI spine scores) and functional ability (BASFI) [14]. No new safety concerns were raised during the trial, however the most common adverse effects noted in the upadacitinib group included elevated creatine phosphokinase [12]. All cases were asymptomatic, and mostly mild and reversible [14]. The homogeneity of this trial population has evaluated the risks and benefits of upadacitinib in biologic-naïve AS patients in a short timeframe; however, it has not evaluated the efficacy or safety in AS patients with prior inadequate responses to biologics nor patients with nr-AxSpA. Ongoing SELECT-AXIS phase 3 trials are afoot, investigating the longer term effectiveness and safety in AS treatment [14].

Key trials in PsA

The use of filgotinib in active PsA was evaluated in a 16-week phase 2, placebo-controlled trial (EQUATOR, NCT03101670) [15]. Patients with polyarticular moderate/severe PsA [as per the Classification for Psoriatic Arthritis (CASPAR) criteria], plaque psoriasis and inadequate responses to csDMARDs, received filgotinib 200 mg OD orally or placebo [15]. Continued use of csDMARDs was permitted if taken for a minimum of 12 weeks prior to screen, on a stable dose before baseline for at least 4 weeks [15]. Concurrent csDMARD use composed 72% and 76% of patients in the treatment and placebo arms, respectively [15]. Filgotinib was found to be significantly more efficacious in achieving the trial's primary endpoint (ACR20) at week 16, when compared with placebo [80% *vs* 33% respectively; response difference of 47% (95% CI 30.2, 59.2; $P < 0.0001$)] [15]. Similar to the other trials, it showed rapid onset action with measurable disease activity improvement, within 1 week of treatment [15].

In those who had not previously received TNFi therapy, filgotinib achieved greater ACR20 responses with a treatment difference of 43% (78% *vs* 35%) compared with placebo [15]. Greater proportions of those taking filgotinib also achieved 50% and 70% improvement in ACR responses (ACR50 and ACR70, respectively) compared with placebo at week 16 [15]. Treatment differences of 33% (95% CI 16.8, 46.2; $P < 0.0001$) and 17% (95% CI 4.9, 29.2; $P = 0.0037$) were observed correspondingly [15].

Disease Activity in Psoriatic Arthritis (DAPSA) scores were significantly improved with filgotinib at week 16, *vs* placebo [15]. Mean change from baseline was −27.9 (S.D. 13.6) and −18.1 (S.D. 19.9), respectively, with LSMD of −12.5 (95% CI −17.0, −8.0; $P < 0.0001$) [15]. Significantly more patients achieved low disease activity or disease remission with filgotinib (DAPSA $\leq$14), compared with placebo [49% and 15%, respectively; 34% treatment difference (95% CI 18.3, 47.7; $P < 0.0001$)] [15]. Disease remission (DAPSA $\leq$4) was achieved by 11% in the filgotinib group and 3% in the placebo group [8% treatment difference (95% CI −1.4, 17.8; $P = 0.0678$)] [15]. At week 16, filgotinib offered significantly greater mean changes in DAS in 28 joints (DAS28) (CRP) from baseline (*vs* placebo) [15]. These changes were −2.0 (S.D. 0.9) and −0.9 (S.D. 1.1), respectively [LSMD of −1.1 (95% CI −1.5 to −0.8; $P < 0.0001$)] [15].

Overall PsA disease control was improved with filgotinib [15]. Mean changes in baseline Psoriatic Arthritis Disease Activity Scores (PASDAS) at week 16 was also greater in the filgotinib group *vs* placebo [LSMD of −1.3 (95% CI −1.7 to −0.9; $P < 0.0001$)] [15]. Significantly more patients achieved PASDAS $\leq$3.2 at week 16 with filgotinib, indicating low disease activity, when

compared with the placebo group [28% treatment difference (95% CI 13.6, 40.9; $P < 0.0001$)] [15].

Filgotinib showed significant beneficial effects on enthesitis and psoriasis [15]. Of the patients with 3% psoriasis-covered body surface area, a greater proportion of the filgotinib group achieved 75% reduction in their skin disease, when assessed by Psoriasis Area and Severity Index (PASI75), compared with placebo at week 16 (30% treatment difference; $P < 0.0001$) [15]. Enthesitis was improved by filgotinib: SPARCC Enthesitis Index mean changes in baseline scores were greater at week 16, compared with placebo (LSMD of −1.4; $P = 0.0310$) [15]. Resolution of enthesitis did not significantly differ between the two groups (12% treatment difference; $P = 0.1583$) [15]. Subsequent exploratory analysis using the Leeds Enthesitis Index, found greater mean change in baseline scores in the filgotinib group *vs* placebo (LSMD of −1.1; $P = 0.0004$), and greater proportions of enthesitis resolution with filgotinib *vs* placebo (26% treatment difference; $P = 0.0089$) [15].

The trial also observed improvements in patient-reported outcomes in the filgotinib group, relating to physical function ($P = 0.0009$), pain ($P < 0.0001$), fatigue ($P = 0.0086$), PsA-related pain intensity ($P < 0.0001$) and HAQ-DI scores ($P = 0.0009$) [15].

The safety profile of filgotinib was favourable; similar rates of adverse events ensued in both treatment and placebo groups [15]. In line with previous selective JAKi trials, EQUATOR found similar effects on laboratory parameters in the use of filgotinib, including elevated haemoglobin and high-density lipoprotein, and decreased platelets [15, 18, 19]. Research suggests that selective JAK1 inhibition may theoretically offer a preferential safety profile, compared with non-selective JAKi [15]. It has been hypothesized that inhibition of JAK1/2 could be associated with elevated platelets and therefore may explain the risk of thromboembolism seen in previous JAKi trials, which may be less associated with more selective JAK1 inhibition [15, 20]. However, a recent review of thromboembolic events (with tofacitinib) observed higher incidence rates associated with other risk factors (mainly for cardiovascular disease and VTE) [21]. Elevated lipid profiles and creatine phosphokinase, and decreased neutrophils were noted in the use of non-selective JAKi [20].

Other adverse effects observed in non-selective JAKi, namely infection and malignancy, has highlighted potential class-specific safety concerns [13, 18–20]. Further data are required to evaluate if these adverse events are more commonly seen in non-selective *vs* selective JAKi.

The role of upadacitinib has been investigated in the treatment of active PsA in two, 24-week phase 3 trials [16, 17]. The SELECT-PSA-1 trial (NCT03104400) assessed the efficacy of upadacitinib in patients with active PsA and previous inadequate responses to at least one non-bDMARD, compared with placebo and adalimumab [16]. Patients with active PsA and (active or previous) psoriasis, on no more than two non-biological DMARDs were randomized to either: upadacitinib 15 mg OD orally; upadacitinib 30 mg OD orally; adalimumab 40 mg s.c. alternate weeks; or placebo [16]. It found significant improvement in ACR20 rates at week 12, with upadacitinib 15 and 30 mg *vs* placebo (70.6%, 78.5% *vs* 36.2%, respectively; $P < 0.001$) [16]. Both doses of upadacitinib were non-inferior ($P < 0.001$) to adalimumab (ACR20 rate 65%), and upadacitinib 30 mg demonstrated superiority compared with adalimumab ($P < 0.001$) [16]. Higher proportions with both doses of upadacitinib achieved ACR50 and ACR70, compared with placebo, and similarly with upadacitinib 30 mg compared with adalimumab [16].

Improvements were observed in all other secondary endpoints with both doses of upadacitinib (*vs* placebo) demonstrating improved PsA symptoms (dactylitis and enthesitis), psoriasis, functionality, pain, fatigue and radiographic progression [16]. Significantly higher proportions of patients with at least 3% psoriasis-covered body surface area at baseline achieved PASI75 with both doses of upadacitinib (15 and 30 mg), compared with placebo (62.6%, 62.4% and 21.3%, respectively; $P < 0.001$), and these results were similar to the improvements seen with adalimumab [16].

Higher percentages achieved minimal disease activity (MDA) and the static Investigator Global Assessment (sIGA) of Psoriasis in the upadacitinib arms (*vs* placebo) [16]. Upadacitinib 15 and 30 mg achieved 36.6% and 45.4% MDA respectively, compared with placebo 12.3% (treatment differences 24.3% and 33.1% respectively; $P < 0.001$) [16]. MDA percentages were significantly greater when comparing upadacitinib 30 mg (45.4%) with adalimumab (33.3%), with 12.1% treatment difference ($P < 0.001$) [16]. Significant improvement in the percentage of patients achieving sIGA of 0 or 1, and at least 2 points improvement from baseline at week 16, was seen with both doses of upadacitinib (15 and 30 mg), when compared with placebo (41.9%, 54% and 10.9%, correspondingly; $P < 0.001$) [16]. Significant improvement was also seen between upadacitinib 30 mg and adalimumab (38.5%), with 15.5% treatment difference ($P < 0.001$) [16]. Upadacitinib engendered significantly higher proportions of patients achieving resolution of enthesitis (Leeds Enthesitis Index = 0) and dactylitis (Leeds Dactylitis Index = 0) at week 24, compared with placebo ($P < 0.001$) [16]. More patients achieved resolution of enthesitis with both doses of upadacitinib, compared with adalimumab ($P < 0.05$) [16].

Upadacitinib (15 and 30 mg) showed greater improvements in HAQ-DI scores and pain scores (at 30 mg), when compared with adalimumab [16]. Minimal clinically important difference cannot be applied mean average scores; therefore, comparing these differences in mean HAQ-DI scores showed significant benefit ($P < 0.001$) [16]. Adverse event rates (namely infection) were higher in all treatment groups compared with placebo, with the upadacitinib 30 mg arm being the highest [16]. There were no cases of opportunistic infections in the placebo and adalimumab arms [16]. There were one and two cases in the upadacitinib 15 and 30 mg arms,

respectively [16]. Similar rates of Herpes Zoster infections were observed in the placebo and upadacitinib arms, however there were no cases in the adalimumab arms [16]. There were no cases of VTE events in the upadacitinib 15 mg arm; one event with upadacitinib 30 mg group; one in the placebo arm; and two events with adalimumab [16]. There was one case each of malignancy in the upadacitinib 15 mg and placebo arms, and three cases were reported each in the upadacitinib 30 mg and adalimumab arms [16]. Therefore, although efficacy seemed to be superior for the 30 mg upadacitinib dose, it is likely that safety concerns will prevent the availability of this dose in clinical practice. The number of serious adverse events in the treatment arms was similar to the placebo group [16].

The SELECT-PSA-2 trial (NCT03104374) similarly evaluated the use of upadacitinib in PsA, however in patients with previous insufficient responses to bDMARDs [17]. Upadacitinib 15 mg OD orally and 30 mg OD orally were compared with placebo over 24 weeks [17]. Its primary endpoint of ACR20 was significantly greater in patients who received upadacitinib 15 and 30 mg, compared with placebo (56.9% and 63.8% *vs* 24.1%; both comparisons $P < 0.0001$) [17]. All secondary endpoints were significantly improved ($P < 0.0001$) in both doses of upadacitinib (*vs* placebo), including HAQ-DI scores, Short Form-36 Physical Component Summary, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Questionnaire, and Self-Assessment of Psoriasis Symptoms (SAPS) [17]. It observed greater percentages in the upadacitinib groups achieving ACR50 and ACR70 at week 12 ($P < 0.0001$) and MDA at week 24 ($P < 0.0001$), when compared with placebo [17]. Upadacitinib similarly showed significantly higher proportions ($P < 0.0001$) attaining PASI75 and sIGA of 0 or 1 (with at least 2 points improvement from baseline) at week 16 (*vs* placebo) [17].

In keeping with SELECT-PSA-1, similar adverse events were seen [16, 17]. Upadacitinib treatment arms saw higher numbers of adverse events [12 (5.7%) and 18 (8.3%) for 15 and 30 mg, respectively] compared with placebo [4 (1.9%)] [17]. Higher frequencies of infection rates were seen with upadacitinib 30 mg [17]. Three cases of malignancy were reported in each upadacitinib arm, and one myocardial infarction and one pulmonary embolism (both adjudicated) were reported in the upadacitinib 15 mg arm [17]. Both trials have shown upadacitinib to be efficacious in the treatment of active PsA, however safety concerns exist with its use, which appear to be dose-dependent.

Summary

Selective JAK1 inhibitors have shown to be an exciting new mode of action in the treatment of AS and PsA. They have shown multi-faceted efficacy in different measures of SpA disease activity with rapid onset action. While there are potential dose-dependent side effects, their safety profile seems to be positive compared with other non-selective JAKi, in the limited duration of data on this class of drugs. JAK1 inhibitors offer a promising mechanism of treatment in patients with active disease and previous inadequate responses (or contraindications) to NSAIDs, csDMARDs and/or bDMARDs. Further long-term registry data and larger trials are required for evaluating the efficacy and safety of selective JAK1 inhibitors in SpA. A phase 3 trial investigating filgotinib is already underway and will optimize our interpretation of JAK1 inhibitors. Research is also required to evaluate selective JAK1 inhibition in the greater spectrum of SpA, particularly nr-AxSpA.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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