Janus kinase inhibitors for the treatment of psoriatic arthritis

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Abstract

Psoriatic arthritis (PsA), a systemic disease, has multi-domain musculoskeletal pathologies along with dermatological manifestations. The current recommendations and the standard of care for the treatment of PsA is to address the domain-based pathologies and the disease severity of the six clinical domains unique to PsA, namely, arthritis of the large and small joints, skin involvement, nail involvement enthesitis, dactylitis and axial disease. With currently available therapies, there are good numbers of primary/secondary non-responders and there are added concerns because of intolerance and adverse effects. In that respect, JAK/STAT inhibitors bring new options for many such patients with psoriasis and PsA. Here, we will discuss currently approved JAK inhibitors for PsA and the others which are in different phases of development, including the TYK2 inhibitors.

Key words: psoriatic arthritis, psoriasis, JAK-1/2/3 inhibitors, TYK2 inhibitors

Introduction

Clinically, psoriatic arthritis (PsA) is a multi-domain musculoskeletal disease presenting along with psoriasis and other comorbidities including hypermetabolic syndrome.[1–7] It is a chronic and progressive disease. If not treated at an early stage, it is likely to lead to permanent joint damage. PsA affects an array of musculoskeletal structures such as the entheses, the peripheral joints and axial joints and the tendon sheaths, and may be characterised by synovitis, sacroiliitis/spondylitis, enthesitis, fasciitis and dactylitis.[1,2,5–7] Extra-articular manifestations include psoriasis, IBD (inflammatory bowel disease), uveitis and fatigue. These may occur as isolated manifestations or may present together in the same individual.

Prevalence estimates for PsA in patients with psoriasis vary considerably from 6–40%, depending on the definitions used such as diagnostic codes, whether diagnosed by a dermatologist or rheumatologist, populations measured, etc.[3,5,6,8,9] Typically, skin disease precedes joint involvement with a lag time of about 10 years, though the opposite or simultaneous occurrence is possible.[9,10] Therefore, routine screening for PsA in patients with psoriasis in dermatology clinics is critical for early diagnosis.

The current recommendations for the treatment of PsA suggest a domain-based evaluation for the disease severity of the six clinical domains unique to PsA, namely, arthritis of the small and large joints, axial disease, enthesitis, dactylitis, nail involvement and skin changes of psoriasis. Based on these evaluations, treatment guidelines have been provided by American College of Rheumatology (ACR)/ National Psoriasis Foundation (NPF), Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and European Alliance of Associations for Rheumatology (EULAR).[11–14] Non-steroidal anti-inflammatory drugs (NSAIDs) are most

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Table 1: Currently available DMARDs effective in the treatment of Psoriatic Arthritis

Drug class	Name of the drugs
Commonly used Conventional DMARDs	Methotrexate Leflunomide Sulfasalazine Hydroxychloroquine-Restricted use in PsA as it may flare psoriasis Cyclosporine-Compared to psoriasis not much used in PsA
Biologic DMARDs	Tumour Necrosis Factor (TNF) inhibitors: etanercept, adalimumab, golimumab, infliximab, certolizumab pegol and associated biosimilar IL-17 inhibitors: secukinumab, ixekizumab (IL 17monoclobal Ab), brodalumab (IL-17 receptor blocker) IL-12/23 inhibitors: ustekinumab (targeting p40 subunit of IL-12 and IL-23) IL-23 inhibitors: tildrakizumab, guselkumab, risankizumab (targeting p19 specific to IL-23) Selective T cell co-stimulation blocker: abatacept
Others	Apremilast JAK inhibitors- tofacitinib, upadacitinib

commonly prescribed as initial therapeutic agents for PsA patients, though NSAIDs are not expected to either modify or reduce the disease progression. Systemic corticosteroids are only prescribed in rare circumstances as withdrawal of steroid is a known precipitating factor for flare-up of psoriasis and induction of pustular psoriasis. However, intra-articular corticosteroids in appropriate clinical situation may offer relief of pain in monoarticular arthritis and can be used for refractory joint involvement. In overall clinical practice for psoriatic disease, generally biologic disease-modifying antirheumatic drugs (bDMARDs) are initiated in conditions where methotrexate (MTX), leflunomide and apremilast have failed or are not tolerated by patients. In Table 1, a list of currently used conventional synthetic DMARDs (csDMARDs) and bDARMDs is provided.

Despite remarkable advances in the last 2 decades in the treatment options for psoriatic disease, treating patients with psoriasis and PsA can often be a challenge. In a large proportion of PsA patients, their disease may remain uncontrolled; it has been reported that minimal disease activity (MDA) may only be achieved in 17% of subjects treated with csDMARDS and in 57% of patients treated with bDMARDs.[17] Many such unmet needs have kept us busy to develop novel therapies and novel tools to determine the total inflammatory burden of PsA by targeting the underlying cellular and molecular mechanisms of the disease process of psoriatic disease.[7,14] Janus kinase inhibitors (JAK inhibitors or JAKi) bring a new dimension for the management of an array of autoimmune diseases including treatment for psoriatic disease.[18–20] It is expected that JAKi with its judicious use will provide excellent benefits to a large number of PsA patients.

(JAKi) JAK inhibitors: Novel therapies for psoriatic arthritis

Preclinical translational work

The monitoring role of the JAK-STAT kinase cascades in the pathophysiology of psoriatic disease is still not entirely understood. So far, only a few studies have been conducted to ascertain the molecular mechanisms of the JAK-STAT pathway in the inflammatory proliferative cascades of PsA. The therapeutic effectiveness of tofacitinib has been ascribed to its inhibitory role on T lymphocytes.[21,22] JAK3 is widely expressed in the T cells and in other immune cells. Tofacitinib was primarily designed as a small synthetic organic molecule with an aim to target JAK3 for the treatment of immune-mediated inflammatory conditions.[21] With time, it has been verified that tofacitinib (CP-690,550) also targets JAK1/JAK2 with the potency rank order of tofacitinib: JAK3 > JAK1, JAK2 > TYK2.[23]

Anomalous activation of IL-23/IL-23R is a key element in the pathogenesis of PsA.[24–26] IL-23/IL-23R controls expansion/maintenance and functional maturation of the Th17 cells. Contributions of the Th17 TEM (effector memory) cells along with their signature cytokines IL-17A/IL-17F/IL-22 are now well categorized in the disease process of PsA. As JAK2 and Tyk2 get recruited to the IL-23R, IL23/IL23R-induced JAK/STAT signalling cascade is likely to have a role in PsA. Based on these thoughts, we postulated that: (1) IL-23 prompted JAK-STAT kinase proteins will activate the Th17 cells in PsA and (2) tofacitinib which is known to inhibit JAK-2 will inhibit Th17 cell activation by downregulating the IL-23-induced JAK-2 phosphorylation.[27] To explore this proposal, we designed experiments to detect the JAK/STAT signalling proteins and their functional significance in sorted activated $CD3^+$ T lymphocytes derived from the synovial fluid of inflamed joints and blood of PsA subjects having active disease and healthy controls. Cells were cultured with and without tofacitinib (50 nM).[27] We observed:

1. In the sorted activated CD3+ T lymphocytes from PsA patients, the rIL-23 prompted specific activation of tJAK-2 and STAT-3. Furthermore, we noticed that tofacitinib markedly down regulated phosphorylation of JAK-2 and phosphorylation of STAT-3, the signalling proteins prompted by IL-23/IL-23R.
2. In PsA, the key immune response, the generation/activation of the pathologic CD4+ CD11a+ CD45RO+ IL-17+ TEM Th17 lymphocytes and their proliferation is regulated by the IL-23R prompted JAK-STAT signalling system.

Table 2: Regulatory role of inflammatory cytokines related to the pathogenesis of psoriasis/psoriatic arthritis on JAK-STAT signalling system and their possible contribution to plaque and pannus formation

Ligand	Receptor	Target JAK kinase	Functions
Interleukin-2	IL-2Rα + IL-2Rb + γc	JAK1,2,3	Promotes proliferation and differentiation of effector and memory cells and promotes regulatory T cell development
Interleukin-9	IL-9R	JAK1,3	Promotes survival and activation of T cells including induction of IL-17 and also induces pannus formation
Interleukin-22	IL-22Rα1 or α2 +IL-10R2	JAK1,TYK2	Contributes to both pannus and plaque formation: (i) mitotic to both keratinocytes and the synovial cells and (ii) induces upregulation of IL-6, IL-8 and MMP-3.
Interleukin-23	IL-12Rβ1 + IL-23R	JAK2,TYK2	Induces Th17 cell differentiation and expansion Promotes secretion of IL-17A, IL-17F and IL-22

These observations provided the proof of concept that IL-23-induced JAK/STAT signalling regulates the effector memory Th17 cells in PsA[27]. This may be one of the mechanisms of action for the therapeutic efficacy of tofacitinib in psoriasis and PsA, as shown in Table 2.

Nucleotide polymorphisms in the JAK-STAT pathway, more specifically JAK2 polymorphisms, have been implicated for spondyloarthritis conditions such as in ankylosing spondylitis[28] and in Crohn's disease[29]; thus, polymorphisms in the JAK-STAT signalling system could be another possible mechanism.

In addition, a few studies have been performed to evaluate the regulatory role of JAK-STAT signalling proteins on other non-immune cellular components such as keratinocytes and synovial cells (FLS) which are key components for the pathologic outcomes for the "plaques and pannus" of psoriasis and PsA.[30,31] It has been reported that tofacitinib can inhibit JAK1/JAK2 in PsA explants.[32] This study explains the regulatory role of the JAK-STAT kinase system on synovial cell biology with respect to migration of FLS and upregulation of certain specific FLS chemokines and has demonstrated that tofacitinib could inhibit these. In another study, it was observed that JAK1 and JAK3 were overexpressed in the epidermal layers of psoriasis plaques and further in an *in vitro* psoriasis model, they observed that tofacitinib inhibited expression of phosphorylated JAK1(pJAK1) and phosphorylated JAK3(pJAK3) in the psoriatic keratinocytes.[33]

We also raised the question how fast a JAKi works. To determine the kinetics of changes in the total inflammatory burden following treatment with a JAKi, we evaluated the degree of inflammation (SUVmax) before and after treatment with tofacitinib in the CIA mouse model by using micro-PET imaging. We have observed that tofacitinib acts fast within days; the degree of inflammation (SUVmax) significantly reduced within 6 days when comparing the mice with daily tofacitinib treatment to the untreated mice ($p < 0.001$).[34]

Current status of clinical use of JAKi and TYK2 inhibitor in PsA

The possible mechanisms of action of specific JAKi in PsA are described in the previous section and in Table 2. In this section, we will describe several JAK/TYK2 inhibitors which have prospects for the treatment of PsA including deucravacitinib, filgotinib, tofacitinib and upadacitinib [Table 3].

Tofacitinib ($C_{16}H_{20}N_6O$), a pyrrolopyrimidine, is a pan-JAK inhibitor. In patients with PsA who previously did not have an adequate clinical response with prior DMARD use, a phase III clinical trial has reported that tofacitinib at doses of 5 mg or 10 mg twice daily improved clinical burden of PsA including reduction of pain along with the improvement of several clinical domains characterised by the reduction of tender/swollen joints, arthritis, enthesitis, dactylitis and clearance of psoriasis.[35] This was a phase III, double-blind, randomised, placebo-controlled trial. This study also had a control arm with adalimumab. The ACR20 response in the placebo group was 33%, whereas ACR20 response rate was 50% at month 3 in the 5 mg group ($P = 0.01$; between the 5-mg dose tofacitinib group and the placebo); and in the 10-mg group, ACR20 response was 61% ($P < 0.001$; between the 10 mg tofacitinib

Table 3: Current status of clinical use of JAKi and TYK2 inhibitor in Psoriatic Arthritis

JAKi for psoriatic arthritis	JAK isoforms inhibited	Dose for PsA	Approval status (year of approval)	Efficacy in PsA ACR20 response (References)	Grades of evidence
Tofacitinib	JAK3 > JAK1, JAK2 > TYK2	5 mg twice daily 11 mg daily (extended release tablets)	Approved by FDA (2017)	~60% at week 52 (36)	1b
Upadacitinib	JAK1	15 mg once daily	Approved by FDA (2021)	~70% at week 12 (38)	1b
Deucravacitinib	TYK2	6 mg once daily	Approved by FDA for psoriasis (2022); trials for PsA are in progress	~50% at week 16 (40)	1b
Filgotinib	JAK1	200 mg once daily	Not yet approved for PsA; still in trial	~80% at week 16 (39)	1b

dose and the placebo; In the adalimumab group, the ACR20 response was 52%. However, both arms of tofacitinib (5 mg/10mg) at 12 months did achieve ACR20 response rates around 60%. In another randomised phase III trial, tofacitinib was evaluated in patients with active PsA who did not have an adequate clinical response with TNF inhibitors.[36] Compared to the placebo, treatment with tofacitinib (twice daily) at doses of 5 mg or 10 mg resulted in significantly higher benefit at 3 months. ACR20 response rates were 50%, 47% and 24%, respectively, for 5 mg dose of tofacitinib, 10 mg dose of tofacitinib and the placebo. At 3 months, better benefits in physical function were also observed in the tofacitinib-treated patients; HAQ-DI scores were −0.39 and −0.35, as compared to −0.14 in the placebo group ($P < 0.001$).

Upadacitinib ($C_{17}H_{19}F_3N_6O$) is a selective JAK1 inhibitor. Two phase III trials, SELECT-PsA 1[37] and SELECT-PsA 2[38] have demonstrated the efficacy of upadacitinib in multiple clinical domains of PsA. Data from the SELECT-PsA 1, a phase III trial, where upadacitinib was evaluated with daily doses of 15 mg or 30 mg were compared to daily oral placebo and with the active arm consisting of adalimumab (40 mg/subcutaneously/every 2 week) in bDMARD-naive PsA patients. ACR20 response rate at week 12 was the primary endpoint of this study and this was compared with the placebo group. Both arms of 15 mg and 30 mg doses of upadacitinib achieved the primary endpoint for ACR20 response rates at week 12. ACR20 responses with daily dose of 15 mg and 30 mg of upadacitinib were, respectively, 70.6% and 78.5%, whereas the placebo group had about 36% response[37] and the adalimumab had an ACR response of 65%.

The SELECT-PsA 2 was a phase III 24-week study where upadacitinib was evaluated in bDMARD inadequate responders with daily doses of 15 mg or 30 mg and was compared to daily oral placebo. ACR20 response rate at week 12 was the primary endpoint of this study and this was compared with the placebo group. At week 12, both 15 mg and 30 mg doses of upadacitinib achieved the primary endpoint for the ACR20 response rate. ACR20 responses with daily dose of 15 mg and 30 mg of upadacitinib were, respectively, 56.9% and 63.8% compared to about 24% response in the placebo group.[38]

Filgotinib ($C_{21}H_{23}N_5O_3S$), a JAK1 inhibitor, has also been reported to be effective in PsA. In a randomised, placebo-controlled phase II clinical trial (EQUATOR), patients were randomly allocated (1:1) to oral filgotinib 200 mg once daily or oral placebo once daily for 16 weeks. At week 16, this phase II trial (EQUATOR) observed that in the filgotinib group, 80% achieved an ACR20 response compared to only 33% in the placebo group.[39]

Tyrosine kinase 2 (TYK2) is an intracellular kinase which is also a member of the JAK kinase family. TYK2 mediates signal transduction response for multiple cytokines such as IL-23, IL-12 and interferon α/β. Deucravacitinib ($C_{20}H_{22}N_8O_3$) is a selective TYK2 inhibitor which binds to a regulatory domain of TYK2, whereas, in contrast, the JAK-1/2/3 inhibitors bind to an active site of the kinase domains. A phase II study has reported deucravacitinib to be effective in the treatment of PsA.[40] In this double blind trial, deucravacitinib 6 mg or 12 mg was given orally daily and also had a placebo arm. The primary endpoint for all the arms was ACR20 response rate at week 16. Both the 6 mg and 12 mg doses demonstrated significant efficacy for deucravacitinib. This oral selective TYK2 inhibitor in the trial was well tolerated by PsA patients. The ACR 20 responses at week 16 were 52.9%, 62.7% and 31.8%, respectively, for 6 mg dose, 12 mg dose and the placebo. Compared to the placebo, both doses of deucravacitinib also achieved significant improvement in several secondary endpoints which included ACR50/70 and enthesitis responses. No safety signals for venous thromboembolism (VTE) were noted in this study.

Safety and adverse effect

Safety, adverse effect of JAKi, baseline investigations prior to initiation of JAK inhibitors and lab monitoring for JAKi have been discussed in detail in a previous article in this issue. Similar to MTX baseline labs, CBC, LFT, creatinine, hepatitis serologies and lipid profiles need to be ordered. In general, the safety profile of JAKi is observed to be overall good and does not differ much among the different inhibitors. Long-term extension studies suggest JAKi to have an acceptable safety profile though similar to other DMARDs risks for immunosuppression and increased risks for infections may be of concern.[41,42] Reports of the tofacitinib trials suggest that the frequency of malignancies (other than non-melanoma skin cancer) over time remained stable, and it was observed to be of similar range compared to the reports of biologics in the rheumatoid arthritis (RA) patients.[43] Compared to the placebo, increased numbers of DVT and pulmonary embolism (PE) have been observed in some studies in JAKi-treated patients which suggest possibility of higher risks for VTE.[41,44] A recent randomised, open label, non-inferiority safety trial among patients with RA (>50 years age) having at least one cardiovascular risk factor evaluated tofacitinib against TNF; over a median follow-up period of 4 years, this study has identified higher incidence of malignancy and major adverse cardiac events (MACE) among patients treated with tofacitinib compared to a TNF inhibitor.[45] Clinical efficacy was similar in both the groups. TNF inhibitors already carried a black box warning of increased risk of cancer; shortly after this study, the FDA applied this warning to tofacitinib, upadacitinib and baricitinib. The FDA has also narrowed the indications for tofacitinib, upadacitinib and baricitinib from incomplete response to MTX to also include incomplete response to anti-TNF agents in the treatment of RA.[46] Additional long-term trials are needed to better understand how this trial translates to patient outcomes.

Conclusion and Opinion

For psoriatic disease, tofacitinib and upadacitinib are approved for PsA by FDA [Table 3]. Both Tofacitinib and upadacitinib

are approved for axial SpA (ankylosing spondylitis) and it may indicate that these two drugs may also be effective on the axial component of inflammation in PsA patients. Thus, these JAKi are very appropriate for treating both axial and peripheral arthritis of PsA. However, it is an important issue when to introduce JAKi in patients with PsA. EULAR 2019 recommendation for the treatment of PsA has suggested JAKi to be considered after trials of csDMARDs such as MTX, leflunomide and sulfasalazine,;[13] whereas GRAPPA 2022 recommendation suggests that JAKi can even be used in csDMARD-naïve patients. However, GRAPPA has not recommended JAKi in patients with nail involvement.[12] It is important to mention that FDA has narrowed the indications for tofacitinib, baricitinib and upadacitinib from incomplete response to MTX to also include incomplete response to TNF inhibitor.[46]

Efficacy of JAKi remains significantly low for the skin response that is the PASI75 response, compared to the bDMARDs. So, clinicians need to address personalised treatment considering the degree of severity and the spectrum with respect to all the clinical domains of PsA including the skin/nail involvement. In that respect, TYK2, a different intracellular kinase than JAK-1/2/3 which also mediates through IL-23, the critical cytokine for the inflammatory cascades of psoriasis/ PsA, has been targeted for the development of treatment with better efficacy for psoriasis. Deucravacitinib selectively inhibits TYK2. In 2022, this novel kinase TYK2 inhibitor got approved by FDA[47] for its significant efficacy in psoriasis with PASI75 response around 75%[48] and its efficacy in PsA is also getting evaluated as mentioned in the previous section.[40]

The treatment of PsA is constantly evolving as more molecular targets are identified. JAK-STAT/TYK inhibitors can be used along with cDMARDS such as MTX, sulfasalazine and leflunomide, and can also be used with corticosteroids and apremilast. However, there is no recommendation for the combined use of bDMARDS and JAK STAT/TYK inhibitors in PsA or in any other autoimmune diseases. The oral formulation, rapid onset of action and efficacy of JAKi in bDMARD inadequate responders, provides an alternate therapeutic option for the management of severely unresponsive patients with psoriatic disease. This may also lay the foundation of a bright future for the development of other agents that may be used in the treatment for of PsA by targeting the intracellular signalling system.[14,49]

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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