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PSORIASIS (J WU, SECTION EDITOR)

JAK Inhibitors for Psoriasis and Psoriatic Arthritis

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Abstract

Purpose of Review Janus kinase (JAK) inhibitors represent a growing class of medications for the targeted treatment of psoriatic disease that can be administered orally or formulated into topical preparations. This article reviews the utility and clinical significance of JAK inhibitors for the treatment of psoriatic disease—both psoriatic arthritis and plaque psoriasis—as demonstrated in clinical trials.

Recent Findings Tofacitinib, the most widely studied of the JAK inhibitors in psoriatic disease, has demonstrated significant efficacy for the treatment of both psoriatic arthritis and plaque psoriasis. However, while it received approval from the US Food and Drug Association for the former indication, it was denied for the latter. This has not deterred the development of newer JAK inhibitors which hope to provide a balance of efficacy and safety that would allow for their approval. Topical ruxolitinib has also demonstrated efficacy for the treatment of plaque psoriasis.

Summary JAK inhibitors function by blocking the JAK-STAT pathway, which is crucial to the signaling of the numerous cytokines implicated in the pathogenesis of psoriasis. While oral tofacitinib and topical ruxolitinib are the most well-studied medications for this indication, newer JAK inhibitors—filgotinib and upadacitinib, in particular—are proving promising in more recent clinical trials.

Keywords Psoriasis · Psoriatic arthritis · JAK inhibitor · Tofacitinib · Ruxolitinib · Filgotinib · Upadacitinib

Introduction

Psoriasis is a chronic immune-mediated inflammatory dermatosis that affects 1–3% of the global population. It is characterized by a chronic immune dysregulation leading to inflammation and epidermal hyperplasia that results in well-demarcated erythematous plaques. Up to one third of patients with psoriasis also have psoriatic arthritis, a seronegative spondyloarthropathy that presents similarly to rheumatoid arthritis [1]. Both diagnoses can be viewed as clinical manifestations of a larger psoriatic disease spectrum that, like other inflammatory disorders, results in systemic inflammation that has been linked to underlying medical comorbidities and potentially worsened cardiovascular outcomes [2]. Thus, treatment of psoriatic disease is not only important for symptomatic relief but also to ameliorate the underlying inflammation, especially in the case of psoriatic arthritis, which causes permanent joint damage and can be quite disabling.

Existing treatment options for psoriasis include topical therapies (i.e., steroids, vitamin D analogues, retinoids, calcineurin inhibitors, and tar products), phototherapy, systemic immunosuppressants (i.e., methotrexate, cyclosporine), acitretin, apremilast, and targeted biologic therapy against cytokines implicated in the pathogenesis of psoriasis (i.e., TNF-α, IL-12/23, IL-17, and IL-23). The latter have proven to be the most efficacious of the available therapies today but are limited by their parenteral administration. There is still a need for targeted treatment options for psoriasis that can be administered orally and even topically, especially for those with refractory localized disease. Janus kinase (JAK) inhibitors represent potential treatment options that may be able to fill this unmet need in the landscape of psoriasis therapy.

Psoriatic Disease and the JAK-STAT Pathway

Numerous cytokines and cell types are implicated in the pathogenesis of psoriasis. Based on current understanding, naïve T

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cells are differentiated into Th1 or Th17 cells by IL-12 and IL-23, respectively. These cells then go on to produce IL-17, IFNγ, IL-22, and TNFα which are all known to potentiate the psoriatic disease process [3]. Currently approved biologic therapies for psoriasis target TNF-α, IL-12, IL-17, and IL-23. These cytokines function through different signaling pathways, including the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway [4].

The Janus kinases (JAKs) are a type of non-receptor protein tyrosine kinases and have four subtypes: JAK1, JAK2, JAK3, and TYK2. Each member is activated by different cytokine receptors, thereby having unique functional roles. JAK1 responds to interferons, IL-6, and IL-10 receptors. JAK2 is mainly associated with hematopoietic receptors but has also demonstrated an association with IL-12 and IL-23. JAK3 is involved in signaling for receptors with the common chain, which is a component of receptors for cytokines (i.e., IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21) implicated in lymphocyte functioning. TYK2 is associated with interferons, like JAK1, but also associates with IL-12 and IL-23 receptors alongside JAK2 [4, 5].

Once the respective receptors are activated by a cytokine, they induce JAKs to bind to each other in pairs and form dimers. These then autophosphorylate and, in turn, phosphorylate the receptors to allow for STAT to bind. Once bound, STATs get phosphorylated and dimerize. The dimerized STATs then translocate to the cell nucleus where they influence gene transcription. There are six different STATs, allowing for various JAK and STAT pairs and broad downstream effects [5].

Beyond the signaling of the cytokines themselves, the JAK-STAT pathway is heavily tied to the functioning of T cells. STAT1 and STAT4 are involved in the differentiation of naïve T cells to Th1 cells, whereas STAT3 allows for differentiation into Th17 cells [6]. Both of these cell types are implicated in the development of psoriasis. Th17 cells produce IL-22, which has been shown to mediate acanthosis and dermal inflammation in psoriasis by STAT3 activation [7]. IL-17 production by Th17 cells is also augmented by other cytokines through a JAK-STAT pathway [6]. Psoriasis has been demonstrated to be predominantly driven by JAK3 and JAK1 with activation of STAT3 [8]. Thus, the JAK-STAT pathway is inextricably tied to the pathogenesis of psoriasis and, in turn, in its treatment.

JAK inhibitors function by blocking the activation of JAKs, thereby suppressing the inflammatory cascade implicated in autoimmune diseases. Not only do they inhibit signaling of the cytokines involved in psoriatic disease but also inhibit the downstream functions of Th1 and Th17 cells that potentiate the disease process. Each JAK inhibitor is unique in the JAK it preferentially blocks.

JAK Inhibitors in Psoriatic Arthritis

Psoriatic arthritis (PsA) is believed to be a member of the seronegative spondyloarthropathies, with others being ankylosing spondylitis, IBD-associated arthritis, and reactive arthritis. It can present with arthritis of the small and medium-sized joints, dactylitis, enthesitis, spondylitis, and uveitis [9]. Animal models have demonstrated that the disease originates at sites of high mechanical stress, namely, the entheses or the sacroiliac joint, and then affects surrounding tissues [10]. As with skin psoriasis, IL-23 and IL-17 are believed to be key mediators of this inflammatory process [11]. As discussed above, the JAK-STAT pathway not only accounts for the signaling of these cytokines but also influences their production by inhibiting T cell differentiation.

Tofacitinib, a selective JAK1 and JAK3 inhibitor, has been well-studied in PsA and was approved for the treatment of active psoriatic arthritis in patients who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs) [12]. Two pivotal phase 3 trials are responsible for this approval. The first of these was the OPAL Broaden trial, a double-blind, active-controlled and placebo-controlled, phase 3 trial that took place over a 12-month period. Patients were randomly assigned to receive either tofacitinib orally 5 mg twice daily, tofacitinib 10 mg orally twice daily, adalimumab 40 mg subcutaneously biweekly, placebo with a blinded switch to tofacitinib orally 5 mg twice daily at 3 months, or placebo with a blinded switch to tofacitinib orally 10 mg twice daily at 3 months. To qualify for this study, patients had to have demonstrated an inadequate response to DMARDs and should not have taken any TNF inhibitors in the past. The primary endpoint in this study was the proportion of patients who had $\geq$ 20% improvement based on the criteria set forth by the American College of Rheumatology (ACR20). Results demonstrated ACR20 scores for tofacitinib (50% at 5 mg BID and 61% and 10 mg BID) well above that of placebo (33%) and comparable to that of adalimumab (52%) [13••].

The OPAL Beyond trial, a 6-month, randomized, placebo-controlled, double-blind, phase 3 trial evaluated the use of tofacitinib in patients with an inadequate response to TNF inhibitors. Patients were randomly assigned to receive either tofacitinib orally 5 mg twice daily, tofacitinib 10 mg orally twice daily, or placebo with a blinded switch to one of the two experimental regimens at 3 months. The primary endpoint for this study was the same for that of the OPAL Broaden study. Results demonstrated ACR20 scores for tofacitinib (50% at 5 mg BID and 47% at 10 mg BID) that were significantly above that for placebo (24%) at 3 months, with similar results seen for patients receiving tofacitinib continuously for 6 months. The lower response rate for the group receiving the 10 mg dose of tofacitinib may have been attributed to

a higher mean number of tender and painful joints at baseline [14••].

The safety and efficacy of tofacitinib at 36 months was upheld by the OPAL Balance trial, an open-label, long-term extension (LTE) study of OPAL Broaden and OPAL Beyond [15].

Other JAK inhibitors have also been evaluated for the treatment of psoriatic arthritis. Filgotinib, a selective JAK1 inhibitor, was evaluated in the EQUATOR trial. This was a randomized, double-blind placebo-controlled phase 2 trial. Participating patients had active moderate-to-severe PsA, current or previous history of plaque psoriasis, and an inadequate response to at least one DMARD. Patients were randomly allocated to filgotinib 200 mg or placebo orally once daily for 16 weeks. Results from this study were promising, with 80% of patients receiving filgotinib achieving ACR20, well above the 33% in the placebo group. ACR50 was achieved by 47.7% of patients receiving filgotinib 200 mg compared to 15.2% in the placebo group. It remains to be seen whether these results hold up in phase 3 trials, but the early results are very promising [16•].

Upadacitinib, another selective JAK1 inhibitor, is being studied in PsA in two phase 3 trials (SELECT-PsA1 and SELECT-PsA2). The SELECT-PsA2 trial, a randomized, double-blind, parallel-group, placebo-controlled study, released compelling data in October 2019. The safety and efficacy of upadacitinib was evaluated in adult patients with active psoriatic arthritis that failed treatment with at least one DMARD. Patients were randomly assigned to receive upadacitinib 15 mg orally once daily, upadacitinib 30 mg orally once daily, or placebo with a switch to one of the two experimental regimens at 24 weeks. At week 12, ACR20 (the primary endpoint) was achieved by 57% and 64% of patients receiving upadacitinib 15 mg and 30 mg, respectively, as opposed to 24% in the placebo group. At week 16, PASI75 (one of the secondary endpoints) was achieved by 52% and 57% of patients receiving upadacitinib 15 mg and 30 mg, respectively, compared to 16% in the placebo group. No new safety issues were noted, with adverse events similar to those for previous trials of upadacitinib and other JAK inhibitors. SELECT-PsA1 and SELECT-PsA2 are expected to complete in 2023 [17•].

JAK Inhibitors in Plaque Psoriasis

Although JAK inhibitors have been tested even more widely in plaque psoriasis than in PsA, they are not yet approved for this indication. Tofacitinib and ruxolitinib, the latter of which is a selective JAK 1 and JAK 2 inhibitor, are the most widely studied JAK inhibitors in plaque psoriasis, with newer options being tested as well. Unlike in PsA, topical formulations of JAK inhibitors have also been evaluated for the treatment of plaque psoriasis as they are small molecules able to penetrate the epidermis [8].

Tofacitinib

The efficacy of tofacitinib in psoriasis was originally demonstrated by two identical phase 3, multi-site, randomized, double-blind trials: OTP Pivotal 1 and OTP Pivotal 2. These trials evaluated the efficacy of tofacitinib against placebo for the treatment of moderate-to-severe plaque-type psoriasis. Patients were randomly assigned to receive either tofacitinib 5 mg orally twice daily, tofacitinib 10 mg orally twice daily, or placebo. Patients in the placebo group were switched to one of the other two arms at 16 weeks. The primary endpoint in this study was the proportion of patients who had $\geq$ 75% improvement in the Psoriasis Area and Severity Index (PASI75) receiving a Physician Global Assessment (PGA) score of clear or almost clear (PGA response). At week 16, the PGA response for patients receiving tofacitinib 5 mg (41.9–46.0%) and tofacitinib 10 mg (59.1–59.2%) was significantly higher than those receiving placebo (9.0–10.9%). PASI75 responses were also higher in the tofacitinib 5 mg (39.9–46.0%) and tofacitinib 10 mg (59.2–59.6%) groups than in those receiving placebo (6.2–11.4%). This response was also noted to be dose dependent [18]. Later analysis of data from the same trials demonstrated sustained efficacy through 2 years with tofacitinib therapy [19]. Data from these two trials also demonstrated that tofacitinib greatly improved nail psoriasis at week 16 as measured by the proportion of patients achieving greater than 50% reduction in Nail Psoriasis Severity Index (NAPSI) scores, and the results were maintained at 52 weeks [20].

A randomized, double-blind, phase 3 study conducted in Japan yielded similar results to its American counterpart, with a significant majority of patients achieving PASI75 with tofacitinib at both 5 mg twice daily (62.8%) and 10 mg twice daily (72.7%). This study had an open-label period after the 16-week mark at which point providers could increase the dose of patients in the 5 mg twice daily arm. With this change, there was a 5% increase in the proportion of patients with a PASI75 response. These responses were also sustained through week 52. Adverse events were similar to those seen in previous studies, with 4.3% of patients experiencing serious adverse events and 3.2% with herpes zoster, the latter being more common in patients taking 10 mg twice daily [21].

The efficacy of tofacitinib after withdrawal and retreatment was evaluated in a phase 3 study. Participants were first treated with tofacitinib 5 mg twice daily or 10 mg twice daily for 24 weeks. Those with a positive response to the medication were then reassigned to receive placebo or continue with original regimen. In the retreatment phase, participants were switched back to their initially randomized tofacitinib doses for an additional 16 weeks. Those who received medication

continuously demonstrated better efficacy with 63.0% in the 5 mg BID group and 73.8% in the 10 mg BID group regaining or maintaining at PASI75 response at the end of retreatment. Of those participants that were reassigned to placebo during the treatment withdrawal period, 48.0% of patients in the 5 mg BID group and 72.5% of patients in the 10 mg BID group were able to regain or maintain a PASI75 response after 16 weeks of retreatment. This suggests that continuous treatment is the most efficacious way of administering tofacitinib therapy but that it remains efficacious in most patients who experience a relapse [22].

In a landmark, phase 3 trial, the efficacy of tofacitinib was directly compared to that of etanercept in patients with moderate-to-severe plaque-type psoriasis. This was a multicenter, double-blinded, placebo-controlled, 12-week non-inferiority trial. Patients were randomly assigned to receive either tofacitinib 5 mg orally twice daily, tofacitinib 10 mg orally twice daily, etanercept 50 mg subcutaneously biweekly, or placebo. Patients who had previously failed treatment with a TNF inhibitor were excluded from this study. The primary endpoints were the same as the study described earlier. At week 12, results demonstrated that tofacitinib dosed at 10 mg BID (PASI75 of 63.6%) was non-inferior to etanercept 50 mg BIW (PASI75 of 58.8%) but tofacitinib dosed at 5 mg BID (PASI75 of 39.5%) was not. This was the first study to report non-inferiority of an oral agent to an injectable biologic therapy [23].

An analysis across six clinical trials of tofacitinib demonstrated that the benefit-risk profile for tofacitinib is similar to that of other systemic agents, with the caveat being higher rates of herpes zoster seen in patients treated with tofacitinib. However, the oral route of administration may be preferred by patients over the parenteral administration of other biologic agents and the possibility of injection- or infusion-site adverse events, especially given the presence of effective vaccines for herpes zoster [24•]. The FDA declined to approve tofacitinib for treatment of plaque psoriasis given the above data, citing safety concerns and issuing a complete response letter requesting further studies be performed in 2015, and it remains to be seen whether an approval may eventually be granted.

Topical formulations of tofacitinib have been evaluated for their use in psoriasis but have had conflicting results. The earliest reported trial evaluating the utility of topical tofacitinib in plaque psoriasis demonstrated efficacy. In this vehicle-controlled phase 2a study, 71 patients with moderate-to-severe plaque psoriasis were randomly assigned to receive either 2% tofacitinib ointment 1, vehicle 1, or 2% tofacitinib ointment 2, vehicle 2. Each were applied to a single 300-cm^2 area with a target plaque. The difference between both formulations was that vehicle 1 contained a penetration enhancer. The primary endpoint in this study was the percentage change in Target Plaque Severity Score (TPSS) from baseline at week 4. Results demonstrated significant improvement in the TPSS score for ointment 1 (54.4%) versus vehicle 1 (41.5%) but not for ointment 2 (24.2%) versus vehicle 2 (17.2%). Systemic absorption of tofacitinib was observable in patients, but serologic levels were fourfold lower than those documented with an oral dose of 2 mg twice daily. As such, some adverse events were noted (i.e., nasopharyngitis and urinary tract infections), but none of these were serious [25].

These promising results, however, were not always reproducible. In another vehicle-controlled phase 2a trial by the same authors, patients were randomly assigned to use 2%, 0.2%, or 0.02% tofacitinib or vehicle solution once or twice daily. In this study, there was no significant change in TPSS after 2 weeks. It was speculated that cross-contamination may have been to blame for these results [26].

In 2016, Papp et al. reported on a much larger phase 2b trial comparing the efficacy of tofacitinib ointment at a 2% or 1% concentration applied once or twice daily in 435 patients with mild-to-moderate plaque psoriasis. In this 12-week, randomized, double-blinded, vehicle-controlled study, the primary endpoint was the proportion of patients with a Physician's Global Assessment (PGA-C) of clear or almost clear and > 2-grade improvement from baseline at weeks 8 and 12. Although there was a significant difference between both groups at week 8, there was no significant difference noted at week 12 [27].

Ruxolitinib

Ruxolitinib has been studied in psoriasis only in topical form. Unlike tofacitinib, all trials have consistently demonstrated efficacy in this form. In an early randomized, controlled, double-blind study, 29 patients with limited plaque psoriasis were assigned to receive either vehicle, ruxolitinib cream (0.5% daily, 1.0% daily, or 1.5% twice daily), or an active comparator (calcipotriene 0.005% or betamethasone dipropionate 0.05%). Efficacy was demonstrated for the 1.0% and the 1.5% cream, with the latter being similar onset of effect to the active comparators. There were no serious adverse events noted in this study [28].

In a later study, topical ruxolitinib 1.0% or 1.5% cream applied once or twice daily was evaluated in 25 patients with limited plaque psoriasis for 4 weeks. Patients using ruxolitinib 1.0% once daily and those using ruxolitinib 1.5% cream twice daily demonstrated improvement in their lesions. Skin biopsies demonstrated decreased epidermal hyperplasia and dermal inflammation in most samples, as well as a decrease in immunohistochemical markers of inflammation and markers for Th1 and Th17 cells. However, systemic exposure was limited as analysis of peripheral blood demonstrated no significant inhibition of phosphorylated STAT3 [29].

Other JAK Inhibitors

Baricitinib, a JAK1/JAK2 inhibitor, was evaluated in a randomized phase 2b trial in patients with moderate-to-severe psoriasis. Patients achieved significant improvement in PASI75 rates in the first 12 weeks of treatment, 43% in patients taking 8 mg daily, and 54% in patients treated with 10 mg daily. This response was sustained for the following 12 weeks [30]. Itacitinib, a selective JAK1 inhibitor, was found to result in significant improvements in PGA scores at day 28 at a dose of 600 mg daily in a randomized, double-blind, placebo-controlled, dose-escalation study [31]. GSK2586184, another selective JAK1 inhibitor, demonstrated similar clinical improvement after 12 weeks in a randomized placebo-controlled phase 2a study. At a dose of 400 mg twice daily, the efficacy is similar to that of tofacitinib and baricitinib [32]. Abrocitinib, also a selective JAK1 inhibitor, has also demonstrated promise in the treatment of plaque psoriasis with improvement of symptoms and similar adverse events to other JAK inhibitors [33]. Peficitinib, a JAK1/3 inhibitor, was shown to have dose-dependent improvements in psoriasis severity as measured by PASI scores, PGA scores, body surface area, and histological changes in a phase 2a randomized, double-blind, placebo-controlled, sequential dose-escalation study. There were no serious adverse events reported [34]. BMS-986165, a tyrosine kinase 2 inhibitor, demonstrated a significant dose-dependent improvement in PASI75 rates, with 75% of patients achieving PASI75 at a dose of 12 mg daily [35].

Conclusions

Numerous studies have been conducted to evaluate the utility of JAK inhibitors in psoriasis, both orally and topically. There has been a great deal of evidence supporting the use of oral tofacitinib, with the dosage of 10 mg twice daily yielding clearly superior results than 5 mg twice daily, for the treatment of moderate-to-severe plaque psoriasis. However, it was denied for this indication by the Food and Drug Administration (FDA) in 2015 due to safety concerns that have not been explicitly defined [36]. However, few serious adverse events were reported in patients receiving oral tofacitinib for plaque psoriasis in the reported trials. The most serious of these was herpes zoster in a small number of patients, but the medication carries black box warnings for blood clots and death at the 10 mg twice daily dose. While this may seem alarming, these adverse events are still limited to a small percentage of patients taking tofacitinib 10 mg twice daily in patients treated for other indications [37]. It remains to be seen whether the FDA may continue to apply a conservative approach to the approval and labeling of all JAK inhibitors, but it should be noted that for the most part, major consistent safety concerns have not been noted in any trials thus far.

It is possible that the availability of injectable IL-17 and IL-23 antagonists that are efficacious in treating psoriasis with a limited adverse event profile has slowed the momentum for JAK inhibitors entering the arena of psoriasis treatment. Regardless, there is still a need for more targeted therapies for psoriasis, especially in the form of an oral medication. Given that a JAK inhibitor is already approved for psoriatic arthritis and that the class seems to have consistent efficacy for both skin and joint psoriasis, patients suffering from concomitant plaque psoriasis and psoriatic arthritis can benefit from the dualistic effects of JAK inhibitors.

Topical JAK inhibitors such as ruxolitinib could be a very useful option in the realm of treating limited psoriasis as it provides a means of targeting the aberrant immune pathway resulting in the psoriatic lesion, without the concerns of topical steroids such as cutaneous atrophy, striae, or tachyphylaxis and with limited systemic effects. This localized treatment would bypass most concerns of systemic issues and is a far more elegant solution than applying a topical steroid which suppresses inflammation of all types.

Other JAK inhibitors are being tested in psoriasis, many of which are demonstrating efficacious outcomes. While it remains to be seen whether tofacitinib may ultimately receive approval by the FDA for treatment of moderate-to-severe plaque psoriasis, these newer agents may be able to overcome this standstill limiting the entry of JAK inhibitors into the realm of psoriasis treatment. These JAK inhibitors have the benefit of being more targeted in many cases, and thus the risk/benefit profile may be improved enough to sway the approval of these medications. It is quite possible that JAK inhibitors will be approved for plaque psoriasis in some form within the next decade, allowing for increased tailoring of psoriasis therapy to patient preferences. Given the proven efficacy of JAK inhibitors in atopic dermatitis, alopecia areata, and other dermatological conditions [38], this medication could prove invaluable for patients suffering from multiple dermatological conditions either alone or simultaneously.

Compliance with Ethical Standards

Conflict of Interest Dr. George Han reports grants from Athenex, Boehringer Ingelheim, Bond Avillion, Bristol-Myers Squibb, Celgene, Novartis, MC2, and PellePharm. He also received grants and personal fees from Eli Lilly, Janssen, Pfizer, and UCB. Additionally, Dr. Han received personal fees from Abbvie, LEO Pharma, Ortho Dermatologics, Regeneron, Sanofi Genzyme, and SUN Pharmaceuticals.

Dr. Aakaash Varma declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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