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CURRENT OPINION

JAK Inhibitors for Treatment of Psoriasis: Focus on Selective TYK2 Inhibitors

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Abstract

Despite advances in the treatment of psoriasis, there is an unmet need for effective and safe oral treatments. The Janus Kinase–Signal Transducer and Activator of Transcription (JAK–STAT) pathway plays a significant role in intracellular signalling of cytokines of numerous cellular processes, important in both normal and pathological states of immune-mediated inflammatory diseases. Particularly in psoriasis, where the interleukin (IL)-23/IL-17 axis is currently considered the crucial pathogenic pathway, blocking the JAK–STAT pathway with small molecules would be expected to be clinically effective. However, relative non-specificity and low therapeutic index of the available JAK inhibitors have delayed their integration into the therapeutic armamentarium of psoriasis. Current research appears to be focused on Tyrosine kinase 2 (TYK2), the first described member of the JAK family. Data from the Phase II trial of BMS-986165—a selective TYK2 inhibitor—in psoriasis have been published and clinical results are encouraging, with a large Phase III programme ongoing. Further, the selective TYK2 inhibitor PF-06826647 is being tested in moderate-to-severe psoriasis in a Phase II clinical trial. Brepocitinib, a potent TYK2/JAK1 inhibitor, is also being evaluated, as both oral and topical treatment. Results of studies with TYK2 inhibitors will be important in assessing the clinical efficacy and safety of these drugs and their place in the therapeutic armamentarium of psoriasis. This article reviews current data on the impact of JAK inhibitors in the treatment of adult patients with moderate-to-severe psoriasis.

Key Points

Blockade of the JAK/STAT signalling pathway with small molecules (JAK inhibitors), in particular TYK2 inhibition, seems promising to fulfil an unmet need for safe and effective oral treatments for psoriasis and psoriatic arthritis.

Selective (BMS-986165 and PF-06826647) and non-selective (Brepocitinib) TYK2 inhibitors are showing promising efficacy and safety results in the treatment of psoriasis.

Ongoing clinical trials will be important to place this class of drugs in the therapeutic armamentarium of psoriasis.

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1 Introduction

Psoriasis is a chronic, inflammatory, immune-mediated, and debilitating skin disease, with a high impact on patients' quality of life [1]. Although its pathogenesis is complex and not yet fully understood, the interleukin (IL)-23/IL-17 axis is currently considered to be its main pathogenic pathway [2–4].

In recent years, several biologic drugs targeting this specific signalling pathway have been developed, with encouraging results [5–22]. However, the need for parenteral administration (intravenous or subcutaneous), risk of immunogenicity, potential adverse effects and loss of efficacy over time, justifies the search for further therapeutic solutions.

The development of small molecules blocking intracellular signalling pathways has evolved in recent years. Compared to biologic agents, these small molecules are easier to synthesise, less expensive to produce and can be administered orally or topically [23], which is associated with greater patient convenience and improved quality of life [24]. Also, oral administration can potentially reduce the cost of healthcare support for outpatient and inpatient care services [24].

Conventional oral therapies (such as methotrexate, cyclosporine, acitretin), are associated with several side effects, drug

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interactions, and long-term toxicity. Apremilast, a phosphodiesterase-4 (PDE4) inhibitor approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of moderate-to-severe psoriasis [25] has shown limited efficacy [26]. Thus, it is necessary to develop other orally administered therapies.

The Janus Kinase–Signal Transducer and Activator of Transcription (JAK–STAT) signalling pathway is an intracellular signalling system through which extracellular factors control gene expression [27, 28]. Knowledge about this pathway has increased over the years, with a growing understanding of the importance of blocking JAK–STAT pathway-specific constituents in several immune-mediated diseases [29, 30]. Specifically, in psoriasis and psoriatic arthritis (PsA) blocking the JAK–STAT pathway with oral JAK inhibitors (JAKi) appears to result in beneficial clinical outcomes [31–48].

This article aims to review the current knowledge on the impact of JAKi in the treatment of adult patients with moderate-to-severe psoriasis, with particular focus on selective Tyrosine Kinase 2 (TYK2) inhibitors.

2 JAK–STAT Signalling Pathway

The JAK–STAT pathways play a role in intracellular signalling of cytokines in a variety of cellular processes, and are important in both normal and pathological states such as immune-mediated inflammatory diseases, including psoriasis and PsA.

The coupling of a circulating cytokine, such as a specific interferon (IFN) or interleukin (IL), to its receptor on the cell surface triggers a conformational change of the receptor, activating and recruiting a combination of two JAKs [27, 49, 50]. Consequently, JAKs phosphorylate the receptor, allowing STAT proteins to attach, become phosphorylated and dimerised [51]. When dimerised, STAT proteins can translocate to the cell nucleus and alter gene expression [51] (see Fig. 1).

There are four different types of JAK proteins (JAK1, JAK2, JAK3, and TYK2) and seven different STAT proteins (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6). Each STAT protein can bind to various members of the JAK family [27, 52, 53].

All JAK proteins play an important role in mammals. Studies in mice with JAK1-deficiency revealed severely compromised lymphopoiesis and insufficiency to respond to both type I and II IFNs, with lethal outcome [54]. There are no reports of human beings with JAK1-deficiency [54]. JAK1 pairs either with JAK2, JAK3 or Tyk2, and it mainly transduces signals from IFN-α, IFN-γ, IL-6, and IL-10 receptors.

JAK2 is mainly associated with the critical functions of induction and regulation of erythropoiesis [55]. JAK2 pairs with itself, JAK1 or TYK2, and is crucial to transmit signals for receptors of cytokines such as erythropoietin, thrombopoietin and haemopoietic cell development cytokines as well as IL-12 and IL-23 receptors. Even though primitive erythrocytes were found in JAK2-deficient mice, the cell count was severely reduced, affecting effective erythropoiesis [55]. Postnatal or adult JAK2 deletion in mice has been noted to result in thrombocytopenia and anaemia, suggesting the role of JAK2 in the development of not only the erythroid but also the megakaryocytic components of bone marrow [56, 57]. There are no reports of humans with a loss of function of the JAK2 protein. On the other hand, gain of function of the JAK2 gene is associated with several myeloproliferative diseases, such as polycythaemia vera and essential thrombocythemia [58, 59].

JAK3 is expressed mainly in lymphoid and hematopoietic tissues, in contrast with the ubiquitous expression of the other members of the JAK family [52, 60]. JAK3 only pairs with JAK1 and binds to the common γ-chain cytokine receptor family, which is shared by IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 receptors and is essential for lymphocyte development [60–62]. In humans, JAK3 gene deficiency results in a lack of activity of T, NK, and functional B cells, consequently leading to the development of severe combined immunodeficiency and life-threatening infections [61–63].

TYK2 is involved in intracellular signalling initiated by different cytokines, such as type I IFN, IL-6, IL-12, or IL-23 [52, 62, 64]. Loss of activity of TYK2 results in increased risk for severe cutaneous infections by agents such as herpesviridae, staphylococci, and mycobacteria [65]. Conversely, TYK2 deletion in mice leads to increased resistance to autoimmune, allergic, and inflammatory diseases [66–68].

Following ligand (interferons, interleukins, growth factors, hormones) binding and JAK-mediated phosphorylation of their specific receptors, STATs become phosphorylated by JAKs to form homo- and heterodimers. Their complex role in genetic and epigenetic control of transcription [51, 69, 70], is beyond the scope of this review.

The JAK–STAT signalling pathway is involved in the pathogenesis of several inflammatory and autoimmune diseases including rheumatoid arthritis (RA), psoriasis, PsA and inflammatory bowel disease, since many cytokines involved in the pathogenesis of these immune-mediated conditions use JAK–STAT pathways for signal transduction. Several JAKi have been approved for the treatment of RA and PsA, while others are being developed for the treatment of psoriasis.

2.1 JAK–STAT Pathway in Psoriasis

Psoriasis is a skin-related autoimmune disease in which multiple cytokines (e.g. IFN-α, IFN-γ, TNF-α, IL-1, IL-2, IL-6,

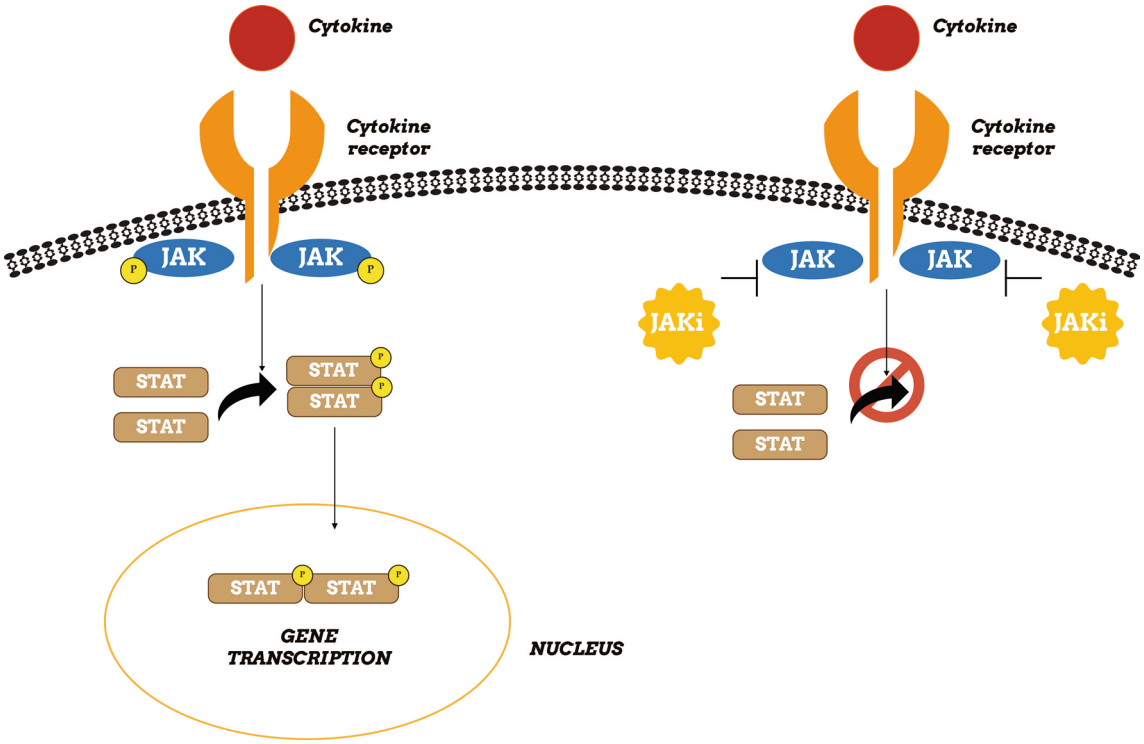

Fig. 1 Schematic representation of Janus Kinase–Signal Transducer and Activator of Transcription (JAK/STAT) pathway and the mechanism of action of JAK inhibitors (JAKi). The JAK–STAT pathway begins with the coupling of a circulating cytokine to its receptor present in the cell membrane. This connection triggers a conformational change of the receptor, which then activates and recruits a combination of autophosphorylated JAKs. JAKs are then responsible for phosphorylating the receptor and create conditions to phosphorylate the STAT proteins, causing their dimerisation. When dimerized, STAT proteins are capable of translocating to the cell nucleus and altering gene transcription. JAKi binds to the Adenosine Triphosphate (ATP)-binding site on JAK, inhibiting the phosphorylation and activation of JAKs. The STAT proteins are not activated, and the remaining cascade is then compromised, resulting in less transcription of pro-inflammatory and pathological genes. Psoriasis-associated cytokines and members of the JAK and STAT families to which they relate are summarised in Table 1

IL-8, IL-12, IL-13, IL-17, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-36) and inflammatory cell populations, including T cells, neutrophils, DCs and others, have been pathogenetically implicated [2–4, 71]. The identification of the IL-23/IL-17 axis as the main pathogenic pathway in psoriasis pathogenesis has had a major impact in our understanding of this disease and changed its therapeutic paradigm [2–4, 71]. Many of the critical pathogenic mediators of psoriasis, including several cytokines of the IL-23/IL-17 signalling pathway, are linked to the JAK–STAT signalling pathway and its upregulation with increased expression of STAT1 and STAT3 has been demonstrated in psoriatic lesional skin compared to normal skin [2, 3, 71–76]. Psoriasis-associated cytokines and members of the JAK and STAT families to which they relate are summarised in Table 1 [77–91].

STAT1 is responsible for signal transduction of both type I (i.e. IFN-α/β) and type II (also known as IFN-γ) IFNs mainly through a JAK1/JAK2-dependent mechanism. IFN-γ has an important role on sensitising keratinocytes and promoting influx of different types of inflammatory cells into lesional psoriatic skin [3]. Its production is also stimulated by IL-12 through a TYK2-dependent mechanism [3]. The increased production of STAT1 leads to the production of multiple pro-inflammatory mediators and the activation and maturation of dendritic cells with subsequent stimulation of Th1 and Th17 cells [73, 74, 92].

STAT3, primarily activated by JAK1, JAK2, and TYK2, is involved in key steps of psoriasis pathogenesis. Through the activation of the JAK2/TYK2 pair induced by IL-23, STAT3 is involved in the induction and differentiation of Th17 cells [72, 93]. STAT3 is also associated with differentiation of Th17 cells and keratinocyte proliferation through a JAK1/JAK2 or JAK1/TYK2 signalling induced by IL-6 [72, 75, 93]. IL-17 plays an indirect activation of STAT3 through the process of inducing the production of IL-19 and IL-36 by keratinocytes, leading to epidermal hyperplasia [3]. Additionally, Th17 cells can produce IL-22, which is also responsible for epidermal hyperplasia

and anti-microbial peptides production through the activation of STAT3 [30, 93–95].

Although IL-23 is closely associated with the activity of TYK2 and JAK2 for downstream signalling events, and IL-12 primarily with TYK2 activity, TNF-α, IL-1, and IL-17 do not activate the JAK–STAT pathway. However, their activity can be indirectly suppressed by the inhibition of the JAK–STAT pathway [30, 94, 95].

Regarding PsA, despite the importance of TNF-α in its pathogenesis, the JAK/STAT pathway seems to play a major role in the development of the disease. The activation and performance of STAT1 and STAT3 appear to play an important role in the onset of a pathological synovial response [96]. This response results from the action of IFN-γ, IL-6, as well as the cytokines enrolled in the IL-23/IL-17 axis, through the activity of JAK1, JAK2 and TYK2 mainly [96].

Therefore, the JAK/STAT pathway regulates several steps in psoriasis pathogenesis, which makes it an interesting target for a new class of small-molecule agents.

3 JAKi Studied in Psoriatic Disease

Several oral JAKi have been studied in psoriasis in recent years [31–48]. Their mechanism of action is illustrated in Fig. 1 and their main characteristics are summarised in Table 2.

3.1 JAK 1/3 Inhibitor: Tofacitinib

Tofacitinib (Xeljanz®) is an oral JAKi that acts primarily on JAK1 and JAK3, and its clinical efficacy and safety in moderate-to-severe psoriasis have been studied in phase II and phase III clinical trials [33, 38–42]. Phase III trials evaluated tofacitinib at 5 mg twice-daily (BID) and 10 mg BID doses. Short term (week 12 or week 16) Psoriasis Area and Severity Index (PASI) improvement of 75% or higher compared to baseline (PASI75) was achieved in approximately 40–64% of patients in the active treatment groups. Greater efficacy was observed with higher doses of tofacitinib, and 10 mg BID regimen was shown to be non-inferior to etanercept. Treatment response was maintained over 2 years of treatment for most patients, with no unexpected adverse events (AEs) [38]. In a study that evaluated treatment withdrawal and retreatment, patients were randomised to receive either tofacitinib 5 mg BID or 10 mg BID for 24 weeks [42]. At week 24, patients who achieved both PASI 75 and Physician's Global Assessment (PGA) of 'clear' or 'almost clear' (PGA response) were re-randomised to receive placebo (withdrawal) or the previous dose of tofacitinib [42]. After 16 weeks, PASI75 response was maintained in a greater proportion of patients receiving either 5 mg BID (56.2%) or 10 mg BID (62.3%) of tofacinib than placebo (23.3% and 26.1%, depending on previous treatment dose, $p < 0.05$ for both comparisons) [42]. After 16 weeks of re-treatment with the previous dosing regimen among patients receiving placebo who relapsed (more than 50% reduction in PASI response compared to week 24) during the treatment-withdrawal period, PASI75 response was achieved in 61% of

Table 1 Psoriasis-associated cytokines and members of the JAK and STAT families to which they relate

1. Cytokines	2. Main JAKs activated	3. Main STATs activated
IFN-γ	JAK1, JAK2	STAT1
IFN-α	JAK1, TYK2	STAT1, STAT2
TNF-α	*Does not directly activate JAK/STAT*	
IL-1	*Does not directly activate JAK/STAT*	
IL-2	JAK1, JAK3	STAT5
IL-6	TYK2, JAK1, JAK2	STAT1, STAT3
IL-8	*Does not directly activate JAK/STAT*	
IL-12	TYK2, JAK2	STAT4
IL-13	TYK2, JAK1, JAK2	STAT3, STAT6
IL-17	*Does not directly activate JAK/STAT*	
IL-18	*Does not directly activate JAK/STAT*	
IL-19	JAK1, JAK2	STAT1, STAT3
IL-20	JAK1, JAK2	STAT1, STAT3
IL-21	JAK1, JAK3	STAT1, STAT3, STAT5
IL-22	TYK2, JAK1	STAT1, STAT3, STAT5
IL-23	TYK2, JAK2	STAT1, STAT3, STAT4
IL-36	*Does not directly activate JAK/STAT*	

Table 2 Characteristics of oral JAKi and their position in psoriatic disease

Drug, company	Main selectivity	Approved indications	Phase of clinical trials in plaque psoriasis	Phase of clinical trials in psoriatic arthritis
Tofacitinib (Xeljanz®), Pfizer	JAK1 and JAK3	Rheumatoid arthritis Psoriatic arthritis Ulcerative colitis	*Phase III* (completed)—not approved for psoriasis and no ongoing clinical trials	*Already approved*
Baricitinib (Olumiant®), Eli Lilly and Company	JAK1 and JAK2	Rheumatoid arthritis	*Phase II* (completed)—no ongoing clinical trials	No clinical trials
Itacitinib, Incyte Corporation	JAK1	None	*Phase II* (completed)—no ongoing clinical trials	No clinical trials
Solcitinibb, GlaxoSmithKline	JAK1	None	*Phase II* (completed)—discontinued investigation in psoriasis	No clinical trials
Abrocitinib, Pfizer	JAK1	None	*Phase II* (completed)—discontinued investigation in psoriasis	No clinical trials
Filgotinib, Galapagos NV	JAK1	None	No clinical trials	*Phase III—2 clinical trials set to start soon*
Upadacitinib (Rinvoq®), AbbVie	JAK1	Rheumatoid arthritis	No clinical trials	*Phase III—2 ongoing clinical trials*
Peficitinib (Smyraf®), Astellas Pharma Inc.	Pan-JAK (moderate selectivity for JAK3)	Rheumatoid arthritis (Japan)	*Phase II* (completed)—discontinued investigation in psoriasis	No clinical trials
BMS-986165, Bristol-Myers Squibb	TYK2	None	*Phase III—4 ongoing clinical trials*	*Phase II—1 ongoing clinical trial*
PF-06826647, Pfizer	TYK2	None	*Phase II—1 ongoing clinical trial*	No clinical trials
Brepocitinib, Pfizer	TYK2 and JAK1	None	*Phase II* (completed)—no ongoing clinical trials	*Phase IIb—1 ongoing clinical trial*

Ongoing clinical studies of TYK2 inhibitors in psoriatic disease are detailed in Table 3

patients receiving tofacitinib 10 mg BID and 36.8% in the group receiving tofacitinib 5 mg BID [42]. In another Phase III trial, 74.1% of patients who reached PASI75 response at short term (week 16) and received 5 mg BID and 79.4% of those who received 10 mg BID maintained their response through week 52 [33].

Regarding safety, clinical trials in psoriasis have shown that tofacitinib was generally well tolerated; the rate of AEs was similar with 5 mg and 10 mg BID, with cytopenia and infections being the most common AEs [33, 38–42].

Regarding PsA, the efficacy and safety of tofacitinib have been evaluated in two randomised, multinational, double-blind, placebo-controlled phase III trials (OPAL Broaden and OPAL Beyond) [44, 45]. Patients received either 5 or 10 mg tofacitinib BID, placebo, or adalimumab in OPAL Broaden only. Patients also received one background conventional synthetic disease-modifying antirheumatic drug (csDMARD). Primary endpoints [i.e. improvement of 20% in the American College Rheumatology score (ACR20) and change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at month 3] showed significant improvements in patients receiving tofacitinib 5 or 10 mg BID versus placebo, and efficacy was maintained at month 6. Significant differences in ACR20 rates were observed as early as week 2. Although none of these studies was designed or had the statistical power to compare the efficacy of tofacitinib with adalimumab, there was no substantial numerical difference in their impact on the primary outcomes. The safety profile was similar to those in previous trials in psoriasis and RA [44, 45, 97].

A topical formulation of tofacitinib has also been tested in chronic plaque psoriasis in three distinct randomised clinical trials (NCT01831466, NCT00678561 and NCT01246583), with a total of 628 participants enrolled in the studies [98]. The results showed only a modest improvement in the disease with this type of formulation, despite the relatively favourable safety profile [98].

There are some special safety concerns related to the drug. A dose-dependent risk of developing herpes zoster was noted, with higher rates of infection occurring in patients receiving tofacitinib compared to those receiving placebo [99]. Gastric perforation was also a complication observed in the group of patients receiving tofacitinib, and further studies are needed to confirm this association [100]. Despite the fact that current evidence on the usage of tofacitinib in RA and PsA in the approved therapeutic dosages (5 mg

BID) seem to indicate that no significantly increased risk of thromboembolic events exists [101–103], the provisional results of an ongoing trial in RA comparing tofacitinib 5 mg BID and 10 mg BID with a TNF-blocker identified an increased occurrence of blood clots and death in the group of patients receiving tofacitinib 10 mg BID, compared to the other two groups. For that reason, patients from this group were allowed to switch and continue treatment with tofacitinib 5 mg BID [104]. Since RA may be associated with increased risk of thromboembolic events [101, 105], long-term studies with a larger number of patients treated with tofacitinib are needed to better understand the development of this complication.

In 2015 the FDA declined to approve tofacitinib for moderate-to-severe psoriasis, indicating that additional safety analyses were required. Tofacitinib is no longer being developed for psoriasis according to Pfizer's drug development pipeline. Currently, oral tofacitinib is both FDA and EMA approved for the treatment of PsA, RA, and ulcerative colitis [106–109].

3.2 JAK1/2 Inhibitor: Baricitinib and Ruxolitinib

Baricitinib (Olumiant®) is an oral JAKi with higher selectivity for JAK1 and JAK2, which has also been studied in patients with moderate-to-severe psoriasis in Phase II trials [43]. At week 12, significantly higher PASI75 response rates were observed in the 8 mg and 10 mg dose groups compared with placebo (42.9%, 54.1%, and 16.7%, respectively, $p < 0.05$) [43].

Although baricitinib was well tolerated in all dosing regimens over 24 weeks, dose-dependent changes in laboratory values [decrease in haemoglobin levels and neutrophil count, increased serum creatinine and high- and low-density lipoproteins, and increased creatine phosphokinase (CPK) levels] have been observed [43].

Baricitinib has also been associated with development of herpes zoster, gastric perforation, and thrombotic events [110, 111]. This association was not significant in studies including patients with RA or psoriasis compared with placebo [102, 112]. However, these AEs should be assessed in more detail in clinical trials with larger numbers of patients. So far, FDA and EMA have approved baricitinib only for the treatment of RA [113]. No clinical studies are evaluating its use in psoriasis or PsA at this time.

Ruxolitinib (Jakafi®/Jakavi®), a JAK1/JAK2 inhibitor, was approved by both FDA and EMA for the treatment of myelofibrosis and polycythemia vera in its oral formulation. However, in psoriasis, its use has only been tested in its topical cream formulation. Three clinical trials (NCT00617994, NCT00820950 and NCT00778700) that enrolled a total of 253 participants evaluated the clinical efficacy and safety of the drug in psoriasis [98]. The published results showed that all treatment groups had a statistically significant improvement in total lesion score compared to vehicle, and that the drug was non-inferior when compared to calcipotriene and betamethasone dipropionate [98]. The studies did not demonstrate any significant AE [98]. Although topical application of the drug is currently being tested for other immune-mediated diseases, such as atopic dermatitis and vitiligo, there are no studies ongoing in psoriasis and it is not approved for psoriatic disease.

3.3 Selective JAK1 Inhibitors: Itacitinib, Abrocitinib, Solcitinib, Filgotinib and Upadacitinib

The clinical efficacy of the JAK1 selective inhibitor itacitinib (INCB039110) in moderate-to-severe psoriasis was studied in a 12-week Phase II trial with 50 patients [34]. Several dosing regimens (100 mg once daily, 200 mg once daily, 200 mg BID or 600 mg once daily) were evaluated and an $\alpha = 0.1$ significance level was used. The mean percentage change from baseline in the static PGA at week 4 (primary endpoint) was statistically superior with itacitinib 200 mg BID and 600 mg once daily compared to placebo [34]. At week 4, PASI75 response rates were 0%, 11.1%, 0%, 22.2% and 27.7% in the placebo, itacitinib 100 mg once-daily, 200 mg once-daily, 200 mg BID, and 600 mg once-daily groups, respectively [34]. A statistically significant difference versus placebo ($p = 0.093$) was observed solely for itacitinib 600 mg once daily [34]. Across all groups, the drug was usually well tolerated, with nasopharyngitis being the most common treatment-related AE [34]. There are currently no ongoing clinical trials involving this drug in psoriasis.

JAK1 inhibitors abrocitinib (PF-04965842) and solcitinib (GSK2586184) have also been evaluated in 12-week phase II clinical trials in patients with moderate-to-severe psoriasis with positive results [36, 37], but they are no longer being tested for psoriasis because solcitinib was discontinued due to AEs, whereas development priorities changed for abrocitinib, with phase III trials for atopic dermatitis currently ongoing.

Filgotinib is being developed and currently tested for PsA, but not for psoriasis. In a Phase II trial, including 131 patients (65 receiving filgotinib and 66 placebo), 80% of patients in the filgotinib group and 33% in the placebo group achieved ACR20 at week 16 (treatment difference 47% [95% CI 30.2–59.6], $p < 0.0001$) [46]. The onset of action of filgotinib was rapid, with measurable improvements in disease activity after 1 week of treatment [46]. Filgotinib was well tolerated and associated with mostly mild-to-moderate AEs. The most common events were nasopharyngitis and headache, occurring at similar proportions in each group [46]. Rates of treatment-emergent AEs and treatment discontinuations due to such events were similar to those of placebo. One case of serious infection (pneumonia) that led to death

was observed in the filgotinib group. Increased haemoglobin and high-density lipoprotein (HDL) levels, stable natural killer cell and lymphocyte counts, and decreased platelet numbers were also reported. No malignancies, thromboembolic events, or cases of opportunistic infections, including tuberculosis, were reported in this study [46].

Upadacitinib (Rinvoq®), an oral JAK1 inhibitor recently approved for the treatment of moderate-to-severe RA [114], is also being tested in patients with PsA, with two ongoing Phase III studies (NCT03104374 and NCT03104400). No clinical trials have been developed to assess its efficacy and safety in psoriasis.

3.4 JAK3 Inhibitor: Peficitinib

A 6-week Phase IIa randomised, placebo-controlled study to evaluate the clinical efficacy and safety of different drug regimens (10 mg BID, 25 mg BID, 60 mg BID, 100 mg BID, 50 mg once daily) of peficitinib (Smyraf®), an oral pan-JAK inhibitor with moderate selectivity for JAK3 over JAK1, JAK2 and TYK2, enrolled 124 patients with moderate-to-severe plaque psoriasis [48]. The mean change in PASI score from baseline to the end of the treatment period (42 days)—primary endpoint—was significantly higher in all the different groups of treatment compared to the placebo group ($p < 0.001$ in all treatment groups) [48]. The proportion of patients who achieved PASI75 at the end of the treatment period was significantly higher only in the groups receiving 10 mg BID, 60 mg BID and 100 mg BID (31.6%, 26.3% and 58.8%, respectively), compared to placebo (3.4%) [48]. No serious AEs were registered [48]. The drug is approved in Japan for the treatment of RA. However, there are no further completed or ongoing clinical trials in psoriatic disease.

3.5 TYK2 Inhibitors: BMS-986165, PF-06826647 and Brepocitinib

The TYK2 gene was first associated with psoriasis susceptibility in a genome-wide association study (GWAS) in 2010 [115]. TYK2 loss-of-function mutation is associated with defects in several cytokine signalling pathways, which are important in the pathogenesis of psoriasis, such as type I IFN, IL-6, IL-10, IL-12, and IL-23 [116]. Even though individuals with deactivating genetic variants of TYK2 are highly protected from some immune-mediated diseases, they do not show an increased risk of hospitalisation due to mycobacterial, viral, or fungal infections, suggesting that inhibiting TYK2 activation may be associated with an optimal balance between efficacy and safety [117].

As knowledge about psoriasis has evolved, the focus on JAK inhibition has shifted, and now seems to be moving toward the JAK family member TYK2.

BMS-986165 is an oral selective TYK2 inhibitor that is being studied for psoriasis, PsA, Crohn's disease, ulcerative colitis, and systemic lupus erythematosus. BMS-986165 showed high selectivity in vitro for the TYK2 pseudokinase domain. In primary human peripheral blood mononuclear cells stimulated with IFN-α and IL-23, BMS-986165 inhibited TYK2-mediated phosphorylation of STAT1 and STAT3, respectively. By contrast, it was considerably less potent (> 100-fold) against receptor-mediated pathways that depended on other JAKs [118].

In a phase I trial involving 108 healthy subjects, BMS-986165 was shown to be safe and well tolerated [31]. Similar non-serious AEs were found in the active and placebo groups (75% and 76%, respectively) and no serious AEs were reported. The most common AEs were headache, nausea, rash and upper respiratory tract infection. BMS-986165 was also evaluated in a 12-week phase II double-blind trial, in which 267 adults with moderate-to-severe psoriasis were randomised to receive the drug (3 mg every other day, 3 mg once daily, 3 mg BID, 6 mg BID, or 12 mg once daily) or placebo [32]. Dosing regimens of 3 mg once daily, 3 mg BID, 6 mg BID and 12 mg once daily proved their efficacy and showed statistical superiority versus placebo regarding PASI75 response rates (39%, 69%, 67%, and 75%, respectively, compared to 7% in the placebo group, $p < 0.05$) [32]. Three serious AEs were reported in three different patients from different active groups—gastroenteritis due to rotavirus, accidental eye injury, and dizziness in a patient with a history of vestibular dysfunction—compared to two serious AEs in one patient in the placebo group [32]. From 55 to 80% of patients in the active treatment groups developed AEs (compared to 51% in the placebo group); nasopharyngitis, diarrhoea, headache, nausea, and upper respiratory tract infection were the most common [32]. No significant changes from baseline in mean values of blood counts or serum levels of lipids, creatinine, liver enzymes or immunoglobulins—IgE, IgM, IgA or IgG—were reported [32]. No cases of herpes zoster infection or cardiovascular events were reported [32].

Three large phase III trials on plaque psoriasis (NCT03624127, NCT03611751, and NCT04036435) comparing BMS-986165 to placebo or apremilast are now ongoing. A smaller phase III clinical trial with 80 Japanese patients with moderate-to-severe psoriasis (NCT03924427) is also under development. In addition to those, one Phase II trial (NCT03881059) to assess the clinical effect of the drug in PsA is in progress (see Table 3). These trials will provide more data about the impact of BMS-986165 in different patients with psoriatic disease.

Another selective TYK2 inhibitor, PF-06826647, is also being tested in moderate-to-severe psoriasis in an ongoing phase II clinical trial (NCT03895372). The results from a

Table 3 Clinical trials in progress with selective (BMS986165 and PF-06826647) and non-selective (Brepocitinib) TYK2 inhibitors in psoriatic disease

Drug, company	Route of administration	Clinical trial	Condition	Phase	Estimated enrolment (number of participants)	Status	Estimated study completion date
BMS-986165, Bristol-Myers Squibb	Oral	NCT03624127	Psoriasis	III	600	Active, not recruiting	July 19, 2020
	Oral	NCT03611751	Psoriasis	III	1000	Recruiting	July 8, 2020
	Oral	NCT03924427	Psoriasis	III	80	Recruiting	November 10, 2020
	Oral	NCT04036435	Psoriasis	III	1680	Recruiting	September 1, 2022
	Oral	NCT03881059	Psoriatic arthritis	II	180	Recruiting	December 31, 2020
PF-06826647, Pfizer	Oral	NCT03895372	Psoriasis	II	160	Recruiting	December 27, 2020
Brepocitinib, Pfizer	Topical	NCT03850483	Psoriasis	IIb	240	Recruiting	May 13, 2020
	Oral	NCT03963401	Psoriatic arthritis	IIb	196	Recruiting	April 27, 2021

phase I clinical trial that also enrolled psoriatic patients have not yet been published.

Even though brepocitinib (formerly known as PF-06700841) is not a selective TYK2 inhibitor (rather a potent TYK2/JAK1 inhibitor), it has been shown to be safe and well tolerated at doses up to 200 mg once daily in a Phase I clinical trial [35]. Thirty patients with psoriasis received PF-06700841 30 or 100 mg or placebo once daily for 28 days; PGA response of clear/almost clear was achieved in 57.1%, 100%, and 0% of patients, respectively [35]. All the AEs were considered to be mild-to-moderate both in healthy subjects and patients with psoriasis [35]. However, a reduction in platelets and reticulocytes count occurred, indicating an inhibition of the EPO-JAK2 pathway by the drug [35].

In a phase IIa trial, 212 patients with moderate-to-severe psoriasis were randomised to receive placebo for 12 weeks or brepocitinib (30 mg once daily or 60 mg once daily) for an induction period of 4 weeks. Then, the group that received the drug switched to either placebo or brepocitinib (10 mg once daily, 30 mg once daily, 100 mg once per week) for a maintenance period of 8 weeks [47]. The primary endpoint was change from baseline in PASI score at week 12, and five treatment arms (brepocitinib 60 mg and then 100 mg once a week; 60 mg and then 30 mg once daily; 30 mg and then 100 mg once a week; 30 mg and then 30 mg once daily; and 30 mg and then 10 mg once daily) achieved significant responses ($p < 0.05$) compared to placebo [47]. The group of patients receiving brepocitinib 30 mg for both induction and maintenance period had the highest PASI75 response rate (86.2%; 90% CI 71.16, 95.15), whereas the group receiving placebo for 12 weeks had the lowest (13.0%; 90% CI 3.65, 30.36) [47]. A total of 149 patients developed AEs, with 6 serious AEs recorded in 5 patients. One patient died during the study (gunshot wound). No herpes zoster events occurred during this study [47].

No other clinical trials with oral brepocitinib in psoriasis are now ongoing. However, a Phase IIb study (NCT03963401) is now recruiting to evaluate the drug efficacy and safety profile in patients with active PsA. Topical application of brepocitinib cream is also being tested in a phase IIb clinical trial involving patients with mild-to-moderate psoriasis (NCT03850483).

4 Discussion

Treatment of psoriasis has evolved rapidly and favourably in recent years, with several biologic drugs acting on different cytokine pathways and achieving promising results. However, there is still an unmet need for effective and safe oral treatments.

Small molecules may have some advantages over biologic agents, particularly the possibility of oral administration, lack of immunogenicity and potentially reduced costs, placing these drugs in a very attractive position for future research in the management of psoriasis.

From the results published so far, inhibition of the JAK–STAT pathway appears to be effective in psoriasis and psoriatic arthritis. However, although several JAK1/2/3 (JAK1/2, pan-JAK with moderate selectivity to JAK3, and selective JAK1 inhibitors) inhibitors are being developed for immune-mediated diseases, their clinical development in psoriasis has been abandoned, mostly due to their efficacy/safety ratio, and only filgotinib and upadacitinib are still being studied in PsA. While tofacitinib has completed a large phase III psoriasis clinical programme, the FDA declined its approval and additional safety analyses were required. Nevertheless, tofacitinib was later approved for treatment of PsA, demonstrating the importance of the JAK–STAT pathway in psoriatic disease and suggesting that JAKi may eventually join the expanding numbers of drugs approved for the treatment of moderate-to-severe psoriasis and PsA, when

additional data on their long-term clinical efficacy, safety, and durability of response become available.

The inhibition of JAK family members may directly and indirectly suppress the activity of multiple cytokines that play a role in the pathogenesis of psoriasis. Thus, differences may be found between wide-ranging inhibition that suppresses the signalling of multiple psoriasis mediators, and selective inhibition that may spare other members of the JAK family and thereby avoid corresponding safety concerns. Indeed, inhibition of JAK1, 2, and 3 has been associated with an increased risk of serious infections and opportunistic infections. Also, dose-dependent changes in laboratory parameters, including lipids, levels of haemoglobin, decreased numbers of lymphocytes, NK cells, neutrophils, and platelets have been observed, as well as cases of venous thromboembolism and gastrointestinal perforation. On the other hand, selective TYK2 inhibitors, that can prevent IL-23/IL-17 axis signalling, have raised significant expectations regarding oral treatment of moderate-to-severe psoriasis. The reported results on clinical efficacy and safety, including those from the phase II clinical trial with BMS-986165, are highly promising. This selective TYK2 inhibitor did not increase the incidence of herpes zoster and thromboembolic events, and the same happened with dyslipidaemia, a common effect of JAK1 inhibitors mediated through IL-6 signalling impairment; thus, BMS-986165 might be considered to belong to a different therapeutic class compared to nonselective JAKi. Data from ongoing studies will clarify whether TYK2 selective inhibitor(s) can be included among the approved drugs for treatment of psoriasis.

5 Conclusion

Oral JAK inhibitors are showing promising efficacy and safety results in the treatment of psoriasis, particularly recent data regarding selective TYK2 inhibitors. Future studies with oral JAKi will be important to place this class of drugs in the therapeutic armamentarium of psoriasis.

Compliance with Ethical Standards

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Conflict of interest Miguel Nogueira has no conflicts of interest. Luis Puig has received consultancy and/or speaker's honoraria from and/or participated in clinical trials sponsored by AbbVie, Almirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, Gebro, Janssen, LEO Pharma, Eli Lilly and Company, Merck-Serono, MSD, Mylan, Novartis, Pfizer, Regeneron, Roche, Sandoz, Samsung-Bioepis, Sanofi, and UCB. Tiago Torres has received consultancy and/or speaker's honoraria from and/or participated in clinical trials sponsored by AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Janssen, Biocad, LEO Pharma, Eli Lilly, MSD, Novartis, Pfizer, Samsung-Bioepis, Sanofi-Genzyme and Sandoz.

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