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REVIEW

New and emerging oral therapies for psoriasis

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Abstract

Psoriasis is a chronic inflammatory skin disease affecting 2–3% of the global population. Traditional systemic treatments, such as methotrexate, cyclosporine, acitretin and fumaric acid esters, have limited efficacy and are associated with significant adverse effects, necessitating regular monitoring and posing risks of long-term toxicity. Recent advancements have introduced biologic drugs that offer improved efficacy and safety profiles. However, their high cost and the inconvenience of parenteral administration limit their accessibility. Consequently, there is a growing interest in developing new, targeted oral therapies. Small molecules, such as phosphodiesterase 4 inhibitors (e.g. apremilast) and TYK2 inhibitor (e.g. deucravacitinib), have shown promising results with favourable safety profiles. Additionally, other novel oral agents targeting specific pathways, including IL-17, IL-23, TNF, S1PR1 and A3AR, are under investigation. These treatments aim to combine the efficacy of biologics with the convenience and accessibility of oral administration, addressing the limitations of current therapies. This narrative review synthesizes the emerging oral therapeutic agents for psoriasis, focusing on their mechanisms of action, stages of development and clinical trial results.

Keywords: A3AR agonists, chronic inflammatory disease, IL-17 inhibitors, IL-23 inhibitors, oral microbiome, oral therapy, PDE4 inhibitors, psoriasis, S1PR1 modulators, small molecules, TNF inhibitors, TYK2 inhibitors.

Citation

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Introduction

Psoriasis is a chronic inflammatory skin disease characterized by the development of silvery, scaly, erythematous plaques that can occur on various parts of the body, including the extensor surfaces.[1] This condition significantly impacts the quality of life of affected individuals, not only due to the physical discomfort and visible lesions but also due to the psychological and social burden it imposes.[1] Moreover, psoriasis is often associated with a range of comorbidities, including psoriatic arthritis, metabolic syndrome, cardiovascular diseases, anxiety and depression, further complicating its management and reducing the overall well-being of patients.[1]

The pathogenesis of psoriasis involves a complex interplay of genetic, environmental and immunological factors. A critical aspect of this disease is the dysregulation of the immune system. Plasmacytoid dendritic cells play a pivotal role by producing IFNα, which activates myeloid dendritic cells. These cells then produce IL-23, which promotes the differentiation and proliferation of T helper 17 (T_H17) cells.[1–3] T_H17 cells secrete a range of pro-inflammatory cytokines, including IL-17, which synergizes with TNF to drive the inflammatory process.[4] This leads to the hyperproliferation of keratinocytes, creating a feedback loop that perpetuates the chronic inflammation characteristic of psoriasis.[1]

Current management strategies for moderate-to-severe psoriasis include a variety of systemic therapies. Conventional systemic treatments, such as methotrexate (MTX), cyclosporine A and acitretin, have been widely used.[3,5] However, these treatments are often associated with limited efficacy and significant safety concerns, particularly long-term toxicity. MTX, for instance, can cause hepatotoxicity, myelosuppression and pulmonary fibrosis, necessitating regular laboratory monitoring and posing risks of long-term cumulative toxicity.[5,6] Cyclosporine A, whilst effective, carries risks of nephrotoxicity and hypertension and requires careful monitoring of renal function and blood pressure.[5,7] Acitretin, a retinoid,

is teratogenic and can cause mucocutaneous adverse effects, dyslipidaemia and hepatotoxicity.[5,8] The need for regular laboratory monitoring and the potential for drug interactions further complicate the management of patients on these therapies.

Biologic therapies have revolutionized the treatment of psoriasis by specifically targeting immune pathways involved in the disease such as TNF and the IL-23–IL-17 axis.[1] These biologics have shown high efficacy and improved safety profiles compared to conventional systemics. However, they come with their own set of challenges such as limited accessibility due to their high costs and inconvenience and needle phobia due to parenteral administration.[2]

In response to these challenges, new targeted oral therapies are being developed. Apremilast, a phosphodiesterase 4 (PDE4) inhibitor approved in 2014, has demonstrated a favourable safety profile, with fewer serious adverse effects compared to traditional systemic therapies, and a moderate efficacy profile.[2,9] More recently, deucravacitinib, a TYK2 inhibitor approved in 2022, has emerged as a promising oral therapy.[2] Deucravacitinib specifically targets the TYK2 enzyme involved in the IL-23–IL-17 pathway, offering a novel mechanism of action with improved efficacy and safety.[2]

The development of these targeted oral therapies highlights the ongoing need for new treatment options for psoriasis. These therapies aim to combine the efficacy of biologics with the convenience and accessibility of oral administration, addressing some of the limitations of both conventional systemic and biologic treatments. As research continues to advance, one can hope that these new drugs will provide new safe, effective and more convenient options for patients with moderate-to-severe psoriasis, ultimately improving their quality of life.

This narrative review aims to comprehensively evaluate the development and clinical potential of novel and emerging targeted oral therapies for moderate-to-severe psoriasis. A review of the published literature was conducted (up until March 2024) using the PubMed database, published abstracts and virtual presentations from scientific meetings, data from industry press releases, and results published on ClinicalTrials.gov using the following keywords (in isolation and/or in combination): "psoriasis", "small molecules", "oral therapy", "TYK2 inhibitors", "PDE4 inhibitors", "IL-17 inhibitors", "IL-23 inhibitors", "TNF inhibitors", "S1PR1 modulators", "A3AR agonists", "oral microbiome" and "chronic inflammatory disease".

New and emerging oral therapies in development for psoriasis

PDE4 inhibitors

The PDE superfamily includes enzyme families responsible for catalysing the hydrolysis of cAMP or cGMP. Amongst the families that specifically target cAMP, the PDE4 family (comprising PDE4A, PDE4B, PDE4C and PDE4D) – the largest and first to be discovered[10] – is preferentially expressed by keratinocytes and immune lineage cells such as lymphocytes.[11] In the pro-inflammatory state characteristic of psoriasis, PDE4, by catalysing the hydrolysis of cAMP in keratinocytes, activates the NF-κB protein complex, which promotes the production of inflammatory cytokines such as IL-2, IL-6, IL-10, IL-12, IL-23, TNF and IFNγ; in addition, the reduction of intracellular cAMP levels leads to decreased activation of PKA, which in turn leads to reduced activation of the CREB transcription factor,[12] inhibiting the production of anti-inflammatory cytokines such as IL-6 and IL-10.[13] Thus, the beneficial role of PDE4 inhibitors in psoriasis therapy is clear – by increasing intracellular cAMP levels, they inhibit the production of pro-inflammatory cytokines and activate pathways that promote an anti-inflammatory response.[2]

In 2014, apremilast became the first orally administered PDE4 inhibitor to be approved by the FDA for the treatment of plaque psoriasis and psoriatic arthritis.[9] Whilst the overall effectiveness of apremilast is just moderate compared to other treatments, it is complemented by its favourable safety profile, ease of oral administration and success in treating difficult cases of psoriasis. This balance has made apremilast a valuable treatment option, particularly for patients looking for a less intensive regimen with fewer adverse effects.[14] Other PDE4 inhibitors are currently being developed for the treatment of psoriasis.[15]

Orismilast

Orismilast, developed by the Danish pharmaceutical company UNION Therapeutics, is a twice-daily oral PDE4 inhibitor whose therapeutic potential is being studied not only for moderate-to-severe plaque psoriasis but also for atopic dermatitis and hidradenitis suppurativa.[16] When its action was evaluated on 13 isoforms of PDE4, orismilast proved to be a 2–5 times more potent inhibitor than apremilast (Table 1), being also preferentially selective for the PDE4B and PDE4D isoforms, which are particularly associated with the inflammatory process.[17]

In a phase IIa clinical trial involving 36 individuals with moderate-to-severe psoriasis, randomly distributed into

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Table 1. PDE4 inhibitor studies on efficacy and adverse effects of oral therapies in psoriasis.

Treatment	Mechanism of action	Treatment groups	Efficacy	Adverse events	Future directions	Notes
Orismilast	PDE4B/ PDE4D inhibitor	Phase IIa: 36 patients, randomized into 30 mg po bid or placebo[18] Phase IIb: 202 patients, randomized into 20 mg po bid, 30 mg po bid, 40 mg po bid or placebo[19]	Preclinical: 2–5 times more potent inhibitor than apremilast[17] Phase IIa: 30 mg po bid at 16 weeks achieved 44.4% PASI75 (compared to 5.6% in placebo)[18] Phase IIb: 20, 30 and 40 mg po bid at 16 weeks yielded PASI reduction of 52.6%, 61.2% and 63.7%, respectively (compared to 17.3% in placebo)[19]	Phase IIa: 30 mg po bid at 16 weeks resulted in 61.1% nausea and 50% diarrhoea (*versus* 5.6% nausea and 0% diarrhoea in placebo)[18] Phase IIb: 20 mg po bid at 16 weeks – 37.5% diarrhoea, 22.9% nausea and 12.5% headache; 30 mg po bid at 16 weeks – 48% diarrhoea, 38% nausea and 26% headache; 40 mg po bid at 16 weeks – 45.3% diarrhoea, 41.5% nausea and 20.8% headache (compared to 3.9% diarrhoea, 3.9% nausea and 5.9% headache in placebo)[19]	No ongoing phase III clinical trials currently[2]	Phase IIb: treatment-emergent adverse effects results in discontinuation of therapy in 20.8%, 20.0% and 39.6% of individuals in the 20, 30 and 40 mg groups, respectively (compared to 3.9% in placebo)[19]
Mufemilast (Hemay005)	PDE4 inhibitor	Phase II: 216 patients, randomized into 15 mg po bid, 30 mg po bid, 60 mg po bid or placebo[20] Phase III: 306 patients randomized to: 60 mg po bid or placebo[21]	Phase II: no results yet from 15, 30 and 60 mg po bid or placebo[20] Phase III: no results yet from 60 mg po bid[21]			
ME3183	PDE4 inhibitor	Phase I: 126 healthy individuals, randomized into 10 mg po bid, 25 mg po bid or placebo[15] Phase II: 132 patients, randomized into 5 mg po bid, 7.5 mg po bid, 10 mg po od, 15 mg po od or placebo[24]	Preclinical: 5–40 times greater efficacy than apremilast[23] Phase II: 5 mg po bid, 7.5 mg po bid and 15 mg po od at 16 weeks achieved PASI75 of 58.3%, 61.5% and 52.0%, respectively (compared to 14.8% in placebo); 10 mg po od achieved 32% PASI75, though not significantly different than placebo[24]	Phase I: 10 and 25 mg po bid yielded treatment-emergent adverse effects of diarrhoea and headache[15] Phase II: most reported adverse effects in 5 mg po bid, 7.5 mg po bid, 10 mg po od and 15 mg po od at 16 weeks were nausea, diarrhoea and headaches[24]	No ongoing phase III clinical trials currently[2]	Phase II: 5 mg po bid, 7.5 mg po bid, 10 mg po od, 15 mg po od and placebo had 2, 4, 2, 3 and 1 patients, respectively, discontinued due to adverse effects[24]

(*Continued*)

Table 1. (Continued)

Treatment	Mechanism of action	Treatment groups	Efficacy	Adverse events	Future directions	Notes
Roflumilast	PDE4 inhibitor	Phase II: 46 patients, randomized into 500 µg po od or placebo[29]	Case study: in a 48-year-old man, 24 weeks of 500 µg po od resulted in PASI100 (total skin clearance)[27] Phase II (PSORRO): 500 µg po od at 12 weeks resulted in PASI75 of 35% (compared to 0% in placebo) and 500 µg po od at 24 weeks resulted in PASI50, PASI75, PASI90 and PASI100 responses of 65%, 44%, 22% and 9%, respectively[29]	Case study: resulted in transient nausea and reduced appetite, and weight loss from 87 to 81 kg (7.4% of body mass)[27] Phase II (PSORRO): most reported adverse effects of transient gastrointestinal symptoms, weight loss, headaches and insomnia[29]	No ongoing studies currently	Case study: patient followed up every 3 months for 18 months and maintained total skin clearance[26] Phase II (PSORRO): 8.7% of patients receiving 500 µg po od discontinued therapy due to gastrointestinal symptoms, vertigo, headache and insomnia[29] Approved by the FDA in 2022 and Health Canada in 2023 for the treatment of psoriasis in adolescents and adults[26]

PASI, Psoriasis Area and Severity Index; PDE4, phosphodiesterase-4.

groups receiving 30 mg of orismilast twice daily or placebo, after 16 weeks, 44.4% of the experimental group achieved PASI75 (indicating a 75% or greater reduction in Psoriasis Area and Severity Index (PASI) scores), compared to only 5.6% in the placebo group (Table 1). The most common adverse effects reported by the experimental group were nausea and diarrhoea (61.1% nausea and 50% diarrhoea *versus* 5.6% nausea and 0% diarrhoea in placebo).[18]

Subsequently, a phase IIb trial was conducted to evaluate the efficacy and safety of different doses of orismilast in the treatment of moderate-to-severe plaque psoriasis (Table 2), in which 202 patients were randomly distributed into four groups, receiving orismilast in twice-daily doses of 20, 30, 40 mg or placebo. After 16 weeks, the PASI reduction rates were 52.6%, 61.2%, 63.7% and 17.3%, respectively. The most reported adverse effects were nausea, headaches and diarrhoea (20 mg po bid at 16 weeks: 37.5% diarrhoea, 22.9% nausea and 12.5% headache; 30 mg po bid at 16 weeks: 48% diarrhoea, 38% nausea and 26% headache; 40 mg po bid at 16 weeks: 45.3% diarrhoea, 41.5% nausea and 20.8% headache; placebo: 3.9% diarrhoea, 3.9% nausea and 5.9% headache). However, these effects led to discontinuation of therapy in 20.8%, 20.0% and 39.6% of individuals in the 20, 30 and 40 mg experimental groups, respectively, demonstrating that the tolerability of orismilast, especially at high doses, may be a limiting factor for treatment.[19]

At the moment, no phase III clinical trials are ongoing regarding the use of orismilast in the treatment of psoriasis, which will be essential to determining its long-term efficacy, safety and tolerability.[2]

Mufemilast

Mufemilast (also known as Hemay005) is a potent oral PDE4 inhibitor developed by the Chinese pharmaceutical company Tianjin Hemay Bio-tech. A phase II clinical trial evaluated the safety and efficacy of this drug in 216 individuals with moderate-to-severe plaque psoriasis, distributed into four groups receiving 15, 30 and 60 mg of mufemilast twice daily or placebo (Table 1). Although the study was completed in 2021, the results have not yet been disclosed.[20]

Subsequently, a phase III clinical trial involving 306 individuals with moderate-to-severe chronic plaque psoriasis was conducted (Table 1). During 16 weeks, 204 of these participants received a twice-daily dose of 60 mg of mufemilast, whilst the remaining 102 participants were given a placebo. At the end of this period, the PASI75 response rate was assessed, followed by a 36-week period during which the placebo group also began treatment with mufemilast. Although the study ended in July 2023, no results have been released yet.[21]

ME3183

ME3183 is an oral PDE4 inhibitor developed by the Japanese pharmaceutical company Meiji Seika Pharma, which is being studied for the treatment of moderate-to-severe plaque psoriasis, atopic dermatitis, chronic obstructive pulmonary disease and inflammatory bowel disease.[22] In preclinical studies, it demonstrated 5–40 times greater inhibition of inflammatory cytokine production, including IL-10, TNF and IFNγ, compared to apremilast (Table 1).[23]

Phase I trials in 126 healthy individuals established the safety and tolerability of ME3183 up to doses of 25 mg daily or 10 mg twice daily (Table 1). The most reported adverse effects were diarrhoea and headaches, typically associated with all PDE4 inhibitors (10 and 25 mg po bid yielded treatment-emergent adverse effects of diarrhoea and headache).[15]

Subsequently, in a phase II clinical trial, 132 participants with plaque psoriasis were divided into groups receiving ME3183 at doses of 5 mg twice daily, 7.5 mg twice daily, 10 mg once daily, 15 mg once daily or placebo for 16 weeks (Table 1). The groups receiving 5, 7.5 and 15 mg achieved PASI75 response rates of 58.3%, 61.5% and 52.0%, respectively, compared to 14.8% in the placebo group. The group receiving a daily dose of 10 mg did not show significant differences compared to placebo. The most reported adverse effects in the experimental groups were nausea, diarrhoea and headaches (5 mg po bid, 7.5 mg po bid, 10 mg po od and 15 mg po od at 16 weeks had adverse effects of nausea, diarrhoea and headaches).[24] Currently, no new clinical trials involving ME3183 in psoriasis are underway.[2]

Roflumilast

Roflumilast (developed by Takeda, and currently manufactured by AstraZeneca) is a PDE4 inhibitor whose oral administration was approved by the FDA in 2011 for the treatment of chronic obstructive pulmonary disease.[25] Additionally, its topical form was also approved by the FDA in 2022 and by Health Canada in 2023 for the treatment of moderate-to-severe plaque psoriasis in adolescents and adults.[26]

In 2021, Egeberg et al. published a case study where a daily oral dose of 500 µg of roflumilast was administered for 24 weeks to a 48-year-old man with plaque psoriasis (Table 1). At the end of this period, the individual showed total skin clearance (PASI100 response).[27] Subsequently, the therapy was maintained, and he was followed up every 3 months for 18 months, consistently maintaining total clearance.[28] The only reported adverse effects during follow-up were transient nausea and reduced appetite, associated with weight loss from 87 to 81 kg (7.4% of body mass).[27]

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Table 2. JAK inhibitor studies on efficacy and adverse effects of oral therapies in psoriasis.

Treatment	Mechanism of action	Treatment groups	Efficacy	Adverse events	Future directions	Notes
Deucravacitinib (BMS-986165)	TYK2 inhibitor	Phase IIa: 267 patients, randomized into 3 mg po bid, 6 mg po bid, 12 mg po od or placebo[15] Phase III (POETYK PSO-1): 666 patients, randomized into 6 mg po od, apremilast 30 mg po bid or placebo[42] Phase III (POETYK PSO-2): 1020 patients, randomized into 6 mg po od, apremilast 30 mg po bid or placebo[43]	Phase IIa: 3 mg po bid, 6 mg po bid or 12 mg po od at 12 weeks resulted in PASI75 rates of 68.9%, 66.7% and 75%, respectively (compared to 6.7% in placebo)[15] Phase III (POETYK PSO-1): 6 mg po od at 16 weeks resulted in PASI75 of 58.4% (compared to 35.1% and 12.7% in apremilast 30 mg po bid and placebo, respectively)[42] Phase III (POETYK PSO-2): 6 mg po od at 16 weeks resulted in PASI75 of 53% (compared to 39.8% and 9.4% in apremilast 30 mg po bid and placebo, respectively)[43] Meta-analysis: 6 mg po od in the long-term (44–60 weeks) had PASI75 of 65.9%, which was similar to 62.8% of adalimumab 40 mg every other week and 68% of ustekinumab 45 or 90 mg[44] Long-term extension trials comparison (POETYK PSO-LTE study of deucravacitinib 6 mg po od and REVEAL OLE study of adalimumab 40 mg every other week): PASI75 response rate to deucravacitinib remained stable (68.1 % to 67.2% from 52 to 114 weeks), whilst that of adalimumab decreased (64% to 54% from 52 to 114 weeks), and the PASI90 response rate to deucravacitinib remained stable (39.4% to 41.3% from 52 to 114 weeks), whilst that of adalimumab decreased (40% to 34% from 52 to 114 weeks) during the second year of treatment[45]	Phase IIa: 3 mg po bid, 6 mg po bid or 12 mg po od at 12 weeks resulted in adverse effects of nasopharyngitis, headaches, diarrhoea, nausea and upper respiratory tract infections[15] Phase III (POETYK PSO-1): most common adverse events in 6 mg po od were nasopharyngitis and upper respiratory tract infections (6.3% for both) and were similar to those with placebo and apremilast 30 mg po bid[42] Phase III (POETYK PSO-2): most frequent adverse event with deucravacitinib 6 mg po od was nasopharyngitis (10.8% of patients)[43]	Currently, the following clinical trials assessing the safety and effectiveness of deucravacitinib for moderate-to-severe psoriasis are underway: Observational: NCT05633264 (post-marketing surveillance), NCT06382987 (RePhlect, patient registry), NCT05744466 (RePhlect), NCT06258668, NCT01848028 (PsoBest, patient registry), NCT05570955 (adherence study), NCT06104644 (DELPHIN) Phase III: NCT06220604 (ICONIC-ADVANCE 2), NCT06143878, NCT04036435 (POETYK PSO-LTE), NCT04772079 Phase IV: NCT05478499, NCT05701995 (ARTISTYK), NCT06042920, NCT06333860, NCT05858645	Phase IIa: 3 mg po bid, 6 mg po bid or 12 mg po od at 12 weeks had no significant changes in serum lipid values or haematological alterations were recorded[15] Phase III (POETYK PSO-1): efficacy improved beyond 16 weeks and was maintained through 52 weeks[42] Phase III (POETYK PSO-2): adverse event-related discontinuations were lower in the deucravacitinib 6 mg po od with 2.7% (compared to 4.7% and 3.5% in apremilast 30 mg po bid and placebo, respectively)[43] Deucravacitinib 6 mg po was approved by the FDA in 2022[46] and the EMA in 2023[15] for moderate-to-severe psoriasis, the first TYK2 inhibitor to be approved[2]

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Table 2. (Continued)

Treatment	Mechanism of action	Treatment groups	Efficacy	Adverse events	Future directions	Notes
Zasocitinib (TAK-279)	TYK2 inhibitor		Phase IIb: PASI75 was significantly higher in 5, 15 and 30 mg po od with 44%, 68% and 67%, respectively (compared to placebo, 6%) and PASI90 was 21%, 45% and 46%, respectively (compared to placebo, 0%). PASI100 was achieved in 33% of patients taking 30 mg po od. No significant difference in 2 mg po od compared to placebo[51]	Phase IIb: most common adverse effects were SARS-CoV-2 infection, diarrhoea and acne[51]	Two phase III clinical trials ongoing to evaluate the efficacy, safety and tolerability in treatment of moderate-to-severe psoriasis compared to apremilast and placebo. One will last 56 weeks, involving about 600 participants, whilst the other trial will last 69 weeks, involving about 1,000 participants. Results expected in the future[52,53]	Phase IIb: changes found in laboratory test parameters were consistent with known effects of allosteric TYK2 inhibition[51]
Jaktinib	JAK1/JAK2/ ACVR1 inhibitor			Phase I: most common adverse effects reported are diarrhoea, dizziness, headaches and, more concerningly, neutropenia. A relationship was established between neutropenia and the dose of the drug administered[57]	Phase I: 200 mg was defined as the maximum tolerated dose for future trials due to dose-dependent neutropenia adverse effect[57] Phase II: 123 participants will be divided into four groups, 50 mg po bid, 75 mg po bid or 100 mg po bid of jaktinib or placebo for 24 weeks. Results expected to be released in the future[58]	

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Table 2. (Continued)

Treatment	Mechanism of action	Treatment groups	Efficacy	Adverse events	Future directions	Notes
TLL-018	JAK1/JAK2/ TYK2 inhibitor		Phase IIa: 20 mg po bid and 30 mg po bid at 12 weeks had ACR50 (American College of Rheumatology 50%) rates of 65.4% and 72%, respectively, which were significantly higher compared to tofacitinib 5 mg po od with 41.7%[60]	Phase IIa: most common adverse effects reported were dyslipidaemia and respiratory infections. No deaths, thromboembolisms or other significant cardiovascular events were reported[60]	Long-term concerns about the adverse effects of tofacitinib were partially responsible for its rejection by the FDA for psoriasis treatment in 2015, and these results highlight TLL-018 as a potential alternative for this condition[2,61] Phase II: the study involves 120 participants divided into four groups: 10, 20, 40 mg po bid or placebo for 12 weeks. Results expected in the future[62]	
ESK-001	TYK2 inhibitor		Phase II (STRIDE): PASI75 at week 12 for all clinically relevant doses. The highest dose, 40 mg po bid, had the greatest efficacy with 64.1% achieving PASI75, 38.5% achieving PASI90 and 15.4% achieving PASI100[65]	Phase I: well tolerated by 100 healthy individuals, with no significant adverse effects reported[64]	Phase II: an open-label extension study is currently underway to evaluate the long-term efficacy and safety of ESK-001 in the treatment of plaque psoriasis[66,67]	
Lomedeucitinib (BMS-986322) and BMS-986202	TYK2 inhibitor		Phase I: study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics is already complete but results are not yet published[15]		Phase II: efficacy and safety of BMS-986322 in the treatment of psoriasis in a phase II clinical trial, with results expected in the future[69] Phase II: study to evaluate the effectiveness and safety of lomedeucitinib in the treatment of moderate-to-severe psoriasis is currently underway with results expected in the future[70]	

PASI, Psoriasis Area and Severity Index.

Subsequently, a phase II clinical trial (PSORRO) in 2022, where 46 individuals with psoriasis were equally divided into two groups, receiving a daily oral dose of 500 µg of roflumilast or placebo (Table 1) showed that after 12 weeks, 35% of individuals in the experimental group achieved a PASI75 response, which did not occur in any individual in the placebo group. After 24 weeks of treatment, the rates of individuals in the experimental group who achieved PASI50, PASI75, PASI90 and PASI100 responses were 65%, 44%, 22% and 9%, respectively. The most reported adverse effects were transient gastrointestinal symptoms, weight loss, headaches and insomnia, leading to two (8.7%) members of the experimental group to discontinue therapy.[29] Since then, no new studies have been initiated on the potential use of oral roflumilast for psoriasis treatment.

JAK pathway inhibitors

The JAK–STAT pathway mediates the intracellular signalling of multiple cytokines, such as IL-6, IL-10, IL-12, IL-17, IL-19, IL-22, IL-23, TNF, IFNα, IFNβ and IFNγ, in both physiological and pathological conditions, and notably in immune-mediated inflammatory diseases such as psoriasis.[2,15,30] Four JAK family proteins (JAK1, JAK2, JAK3 and TYK2) and seven STAT family proteins (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6) have been identified.[15] When a cytokine binds to a type I or II receptor, its conformation changes, recruiting two JAK proteins, which pair to form a dimer. This phosphorylates the activated receptor, allowing the recruitment of two STAT proteins that bind to it; after phosphorylation, they also form a dimer. This dimer is then translocated to the cell nucleus, where it acts as a transcription factor, inducing the expression of genes that produce growth factors and pro-inflammatory cytokines.[2]

Given the significant involvement of the JAK–STAT pathway in the pathogenesis of psoriasis, multiple therapeutic potential drugs have been developed, which, due to their low molecular weight, can be administered orally or topically.[31] The selectivity of JAK inhibitors varies. First-generation drugs targeted two or three JAK proteins, providing a broader therapeutic effect; however, their association with numerous adverse effects led to their non-approval by regulatory entities.[32,33] For example, tofacitinib, an oral JAK1 and JAK3 inhibitor approved by the FDA and EMA for the treatment of rheumatoid arthritis, psoriatic arthritis and ulcerative colitis,[34] was studied for the treatment of psoriasis in phase II and III studies, showing promising results.[15] In a study with 197 participants, individuals receiving twice-daily doses of 2, 5 or 15 mg of tofacitinib experienced PASI75 in 25%, 40.8% and 66.7% of cases, respectively, compared to only 2% in the placebo group; additionally, PASI90 was documented in 22% of individuals receiving any dose of tofacitinib.[35] Its most common adverse effects were known and relatively benign (nasopharyngitis, other upper respiratory tract infections, diarrhoea and headache),[30] but other studies showed that this drug was also associated with dyslipidaemia, infections (pneumonia, appendicitis, urinary tract infections, pyelonephritis, erysipelas, herpes zoster reactivation), cytopenia and pulmonary embolism.[15,30,36] Consequently, in October 2015, the FDA rejected the approval of tofacitinib for the treatment of psoriasis, considering that more studies were needed to evaluate the drug's long-term safety.[37]

Next-generation inhibitors present greater selectivity and fewer associated adverse effects, with mostly targeting only a single JAK protein. More recently, most of the drugs under development are TYK2 inhibitors, which, by mediating IL-12, IL-23 and IFNα signalling, play a key role in the pathogenesis of psoriasis.[32,38,39]

Deucravacitinib

Deucravacitinib is an oral allosteric inhibitor of TYK2. Pharmacologically, it binds to the pseudokinase or regulatory domain (JH2) of TYK2, altering its conformation, which prevents the catalytic activity of the kinase domain (JH1).[40,41] In 2018, a phase IIa study evaluated the efficacy of this drug in the treatment of moderate-to-severe psoriasis (Table 2). After 12 weeks of deucravacitinib administration in doses of 3 mg twice daily, 6 mg twice daily or 12 mg daily, the PASI75 rates were 68.9%, 66.7% and 75%, respectively, compared to 6.7% in the placebo group. All reported adverse effects were considered mild – nasopharyngitis, headaches, diarrhoea, nausea and upper respiratory tract infections (3 mg po bid, 6 mg po bid or 12 mg po od at 12 weeks resulted in adverse effects of nasopharyngitis, headaches, diarrhoea, nausea and upper respiratory tract infections). Additionally, no significant changes in serum lipid values or haematological alterations were recorded.[15] Subsequently, in two phase III clinical trials (POETYK PSO-1 and POETYK PSO-2), deucravacitinib demonstrated superior efficacy to placebo and apremilast (PDE4 inhibitor) at both 16 and 52 weeks, again without significant adverse effects (in POETYK PSO-1, most common adverse events in 6 mg po od were nasopharyngitis and upper respiratory tract infections (6.3% for both) and were similar to those with placebo and apremilast 30 mg po bid; in POETYK PSO-2, most frequent adverse event with deucravacitinib 6 mg po od was nasopharyngitis (10.8% of patients)) (Table 2).[42,43] Recent studies conducted by Armstrong et al. showed that, in the long-term (44–60 weeks), deucravacitinib has a PASI75 rate of 65.9%, similar to biological drugs currently used in the treatment of psoriasis such as adalimumab (62.8%) and ustekinumab (Table 2) (68%).[44] Moreover, when comparing 1-year and 2-year treatment outcomes (upon comparison of POETYK PSO-LTE study of deucravacitinib 6 mg po od and REVEAL OLE study of adalimumab 40 mg every

other week), the PASI75 response rate to deucravacitinib remained stable (68.1% to 67.2%, from 52 weeks to 114 weeks), whilst that of adalimumab decreased (64% to 54% from 52 to 114 weeks), and the PASI90 response rate to deucravacitinib remained stable (39.4% to 41.3%, from 52 to 114 weeks), whilst that of adalimumab decreased (40% to 34% from 52 to 114 weeks) during the second year of treatment (Table 2).[45] Deucravacitinib in daily doses of 6 mg was approved by the FDA in 2022[46] and by the EMA in 2023[15] for the treatment of moderate-to-severe psoriasis, becoming the first TYK2 inhibitor to be approved for this pathology.[2]

Zasocitinib

Zasocitinib (also known as TAK-279) is an oral allosteric inhibitor of TYK2[47] developed by Nimbus Therapeutics and acquired by the Japanese pharmaceutical company Takeda in 2022.[48] Molecularly similar to deucravacitinib, its only difference is a single amino acid in the allosteric binding site, which prevents its binding to JAK1, making zasocitinib about 130,000 times more selective for the JH2 domain of TYK2 than deucravacitinib.[49,50]

In 2023, a randomized, double-blind, placebo-controlled phase II clinical trial evaluated the efficacy, safety and tolerability of zasocitinib in the treatment of moderate-to-severe plaque psoriasis in 259 participants (Table 2). They were divided into five groups, receiving daily doses of 2, 5, 15 or 30 mg of zasocitinib or placebo for 12 weeks. At the end of this period, the rate of individuals with PASI75 response was significantly higher in the groups taking 5, 15 and 30 mg (44%, 68% and 67%, respectively) compared to the placebo group (6%). Additionally, the PASI90 response rate in these same three groups was 21%, 45% and 46%, respectively, compared to 0% in the placebo group. Finally, the study reported that 33% of individuals taking a daily dose of 30 mg of zasocitinib achieved total skin clearance (PASI100 response). The group taking a daily dose of 2 mg did not show significant differences compared to the control group. The most common adverse effects were SARS-CoV-2 infection, diarrhoea and acne. The changes found in laboratory test parameters were consistent with known effects of allosteric TYK2 inhibition.[51]

Currently, two phase III clinical trials are underway to evaluate the efficacy, safety and tolerability of zasocitinib in the treatment of moderate-to-severe psoriasis compared to apremilast and placebo. The first trial will last 56 weeks and involve about 600 participants, whilst the second trial will last 69 weeks and involve about 1,000 participants. The results of both trials are expected to be shared by Takeda in the future.[52,53]

Jaktinib

Jaktinib is a JAK1 and JAK2 inhibitor derived from momelotinib, an inhibitor of not only JAK1/JAK2 but also ACVR1, developed by the Chinese pharmaceutical company Suzhou Zelgen Biopharmaceuticals and approved by the FDA in 2023 and by the EMA in 2024 for the treatment of myelofibrosis.[54,55] Jaktinib is a deuterated form of momelotinib, where one hydrogen atom is replaced by deuterium, one of its isotopes.[56]

In 2020, a phase I clinical trial demonstrated that jaktinib was well tolerated by a healthy, exclusively Chinese population (Table 2). However, adverse effects were reported, the most common being diarrhoea, dizziness, headaches and, more concerningly, neutropenia. A relationship was established between neutropenia and the dose of the drug administered, so a daily dose of 200 mg was defined as the maximum tolerated dose for future trials.[57]

Currently, a phase II clinical trial is underway to evaluate the efficacy and safety of jaktinib in the treatment of moderate-to-severe chronic plaque psoriasis (Table 2). The 123 participants will be divided into four groups, receiving twice-daily doses of 50, 75 or 100 mg of jaktinib or placebo for 24 weeks. The results of the trial are expected to be released in the future.[58]

TLL-018

TLL-018 is an oral drug that acts as a highly specific inhibitor of JAK1 and TYK2 and was developed by the Chinese pharmaceutical company Hangzhou HighlightII Pharmaceutical.[59] By simultaneously inhibiting both proteins, it aims to achieve superior efficacy to other molecules that inhibit only one, whilst also avoiding adverse effects associated with JAK2/JAK3 inhibition such as cytopenia, thrombotic and infectious risks.[2]

A phase IIa clinical trial conducted in 2023 in the field of rheumatoid arthritis demonstrated that individuals with this condition had a better response to twice-daily doses of 20 and 30 mg of TLL-018 compared to tofacitinib (approved for rheumatoid arthritis treatment). Additionally, no deaths, thromboembolisms or other significant cardiovascular events were reported, with the most common adverse effects being dyslipidaemia and respiratory infections.[60] Because long-term concerns about the adverse effects of tofacitinib were one of the main reasons for its rejection by the FDA for psoriasis treatment in 2015,[61] these results highlight TLL-018 as a potential alternative for this condition.[2]

Currently, a phase II clinical trial is underway to evaluate the efficacy and safety of TLL-018 in the treatment of moderate-to-severe plaque psoriasis (Table 2). The study involves 120 participants divided into four groups, receiving twice-daily doses of 10, 20 or 40 mg of the drug or placebo for 12 weeks. The results are expected to be released in the future.[62]

ESK-001

ESK-001 is a highly selective allosteric inhibitor of TYK2 developed by the American biotechnology company Alumis.[63] In a phase I clinical trial, it was well tolerated by 100 healthy individuals, with no significant adverse effects reported (Table 2).[64] The STRIDE phase II clinical trial investigated the efficacy and safety of ESK-001 for treating moderate-to-severe plaque psoriasis, enrolling 228 patients across five dose cohorts (Table 2). The trial met its primary end point, showing significant improvements in PASI75 at week 12 for all clinically relevant doses. The highest dose, 40 mg twice daily, demonstrated the greatest efficacy with 64.1% achieving PASI75, 38.5% achieving PASI90 and 15.4% achieving PASI100. The ongoing open-label extension study further supports these findings, with 90% of patients at the highest dose achieving PASI75 at 16 weeks. ESK-001 has been well tolerated, exhibiting a favourable safety profile with no treatment-related serious adverse events. These findings support the planned phase III trials set to begin in the second half of 2024, underscoring the potential of ESK-001 as a leading oral treatment for psoriasis and other immune-mediated diseases.[65] A phase II clinical trial open-label extension study is currently underway to evaluate the long-term efficacy and safety of ESK-001 in the treatment of plaque psoriasis.[66,67]

Lomedeucitinib (BMS-986322) and BMS-986202

Lomedeucitinib and BMS-986202 are two TYK2 inhibitors that are deuterated forms of deucravacitinib.[68] BMS-986202, developed by the American pharmaceutical company Bristol Myers Squibb, is being evaluated for its efficacy and safety in the treatment of moderate-to-severe plaque psoriasis in a phase II clinical trial, with results expected in the future (Table 2).[69] Moreover, results from a phase I trial that assessed its safety, tolerability, pharmacokinetics and pharmacodynamics have not yet been disclosed (Table 2).[15] A phase II trial to evaluate the effectiveness and safety of lomedeucitinib in the treatment of moderate-to-severe psoriasis is currently underway with results expected in the future (Table 2).[70]

IL-17 inhibitors

IL-17 is the primary cytokine involved in the inflammatory process of psoriasis.[71] Structurally, the IL-17 family consists of six sub-units: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F. Because IL-17A and IL-17F are particularly involved in the signalling of the psoriatic inflammatory process,[72] recent scientific priority has been the inhibition of these specific sub-units.[73,74] Consequently, in recent years, multiple biological drugs targeting IL-17 have been developed for the treatment of psoriasis such as secukinumab, ixekizumab, brodalumab and bimekizumab.[75] Currently, the priority is the development of orally administered molecules targeting this same pathway.[76]

DC-806

DC-806 is an oral small molecule that acts as an inhibitor of the IL-17A sub-unit, developed by the American biotechnology company DICE Therapeutics (acquired in 2023 by Eli Lilly and Company).[2,15] In a phase I clinical trial involving 40 participants, those administered a twice-daily dose of 800 mg of DC-806 exhibited an average PASI reduction of 43.7% after 4 weeks, compared to only 13.3% in the placebo group (Table 3). All adverse effects were classified as mild or moderate with no dose-dependent trend.[77]

In May 2023, a phase IIb clinical trial began to evaluate the efficacy, safety, tolerability and pharmacokinetics of multiple oral doses (not specified) of DC-806 in 229 individuals with moderate-to-severe chronic plaque psoriasis over 12 weeks (Table 3). However, the results of the study have not yet been disclosed.[78]

DC-853 (LY4100511)

DC-853 is a derivative of DC-806, also developed by DICE Therapeutics/Eli Lilly and Company.[2] In March 2024, a phase I clinical trial was initiated to evaluate the safety and tolerability of this drug in single and multiple doses in 30 healthy participants (Table 3). The study is expected to be completed in the future.[79]

LEO 153339

LEO 153339 is an oral IL-17 inhibitor being developed by the Danish pharmaceutical company LEO Pharma.[15] Its safety and tolerability were evaluated in a phase I clinical trial of single ascending doses and multiple ascending doses in 108 healthy individuals (Table 3). Although the study concluded in July 2022, its results have not yet been released.[80]

IL-23 inhibitors

IL-23 is a key cytokine in the pathogenesis of psoriasis promoting the differentiation and proliferation of T_H17 effector lymphocytes.[2] Biologic agents inhibiting this pathway typically target the p19 (guselkumab, risankizumab and tildrakizumab) or p40 (ustekinumab) sub-units of IL-23 and require subcutaneous administration.[81] Currently, small oral molecules with similar mechanisms of action are being developed.[2]

JNJ-2113

JNJ-2113 (also known as JNJ-77242113 and previously PN-235), developed by the American pharmaceutical company Johnson & Johnson Innovative Medicine, is an oral peptide with high affinity for the IL-23 receptor, blocking its signalling and subsequent cytokine production.[82]

Following a phase I clinical trial that evaluated the safety, tolerability and pharmacokinetics of JNJ-2113 in

Table 3. IL-17 inhibitor studies on efficacy and adverse effects of oral therapies in psoriasis.

Treatment	Mechanism of action	Efficacy	Adverse events	Future directions
DC-806	IL-17A inhibitor	Phase I: 800 mg po bid showed PASI reduction of 43.7% after 4 weeks, compared to 13.3% in placebo[77] Phase IIb: evaluated the efficacy, safety, tolerability and pharmacokinetics of multiple oral doses (not specified) in 229 individuals with moderate-to-severe chronic plaque psoriasis over 12 weeks. However, the results of the study have not yet been disclosed[78]	Phase I: all adverse effects were classified as mild or moderate with no dose-dependent trend[77]	
DC-853 (LY4100511)	IL-17A inhibitor			Phase I: initiated to evaluate the safety and tolerability of single and multiple doses in 30 healthy participants. The study is expected to be completed in the future[79]
LEO 153339	IL-17A inhibitor	Phase I: single ascending doses and multiple ascending doses in 108 healthy individuals. Although the study concluded in July 2022, its results have not yet been released[80]		

PASI, Psoriasis Area and Severity Index.

36 healthy individuals,[83] which showed promising results (though not yet published) (Table 4), two phase II trials were initiated.[84] One of them, titled SUMMIT, aimed to compare the efficacy of JNJ-2113 in treating moderate-to-severe plaque psoriasis against placebo in 90 individuals with the condition over 16 weeks; although it was concluded in April 2023, the results have not yet been disclosed (Table 4).[85] In the other trial, named FRONTIER1, 255 individuals with moderate-to-severe chronic plaque psoriasis were divided into six groups, receiving JNJ-2113 at doses of 25 mg daily, 25 mg twice daily, 50 mg daily, 100 mg daily, 100 mg twice daily or placebo for 16 weeks (Table 4).[86] At the end of this period, the PASI75 response rates in the experimental groups were 37.2%, 51.2%, 58.1%, 65.1% and 78.6%, respectively, compared to 9.3% in the placebo group. Additionally, the PASI90 response rates were 25.6%, 26.8%, 51.2%, 46.5% and 59.5%, compared to 2.3% in the placebo group, and PASI100 response rates were 11.6%, 9.8%, 25.6%, 23.3% and 40.5%, compared to 0% in the placebo group. The most reported adverse effects were SARS-CoV-2 infection, nasopharyngitis and upper respiratory tract infection.[87]

The FRONTIER2 study, a phase IIb multicentre, double-blind, long-term extension trial, has provided promising results for JNJ-2113, an investigational oral peptide for moderate-to-severe plaque psoriasis (Table 4). Over 52 weeks, JNJ-2113 sustained high rates of skin clearance, particularly in the 100 mg twice-daily group, which saw PASI75 responses of 78.6% at 16 weeks and 76.2% at 52 weeks. Secondary end points, including PASI90, PASI100 and Investigator's Global Assessment scores, also showed consistent efficacy. Importantly, safety outcomes were favourable and in line with the previous FRONTIER1 study, with 58.6% of patients reporting adverse events such as nasopharyngitis, upper respiratory tract infections and COVID-19, without a dose-dependent increase in these events. These findings underscore the potential of JNJ-2113 as a durable and convenient oral treatment option for patients with moderate-to-severe plaque psoriasis.[88]

Due to the positive results obtained in FRONTIER1 and FRONTIER2, two phase III clinical trials are currently underway. One of these (ICONIC-LEAD) aims to evaluate the long-term (156 weeks) efficacy and safety of JNJ-2113 in a significant group – 684 individuals with chronic plaque psoriasis (Table 4).[89] The other (ICONIC-TOTAL) will focus on 311 individuals with psoriatic plaques in specific regions – scalp, genital area, palms and soles (Table 4).[90] Both studies are expected to conclude in the future.[89,90]

Table 4. IL-23 inhibitor studies on efficacy and adverse effects of oral therapies in psoriasis.

Treatment	Mechanism of action	Efficacy	Adverse events	Future directions
JNJ-2113 (JNJ-77242113, and previously PN-235)	IL-23 receptor inhibitor	Phase I: evaluated the safety, tolerability and pharmacokinetics in 36 healthy individuals but results not yet published[83] despite 'promising' results[84] Phase II (SUMMIT): aimed to compare the efficacy in treating psoriasis against placebo in 90 individuals over 16 weeks; though it was concluded in April 2023, the results have not yet been disclosed[85] Phase IIb (FRONTIER1): 255 individuals with moderate-to-severe chronic plaque psoriasis were divided into six groups: 25 mg po od, 25 mg po bid, 50 mg po od, 100 mg po od, 100 mg po bid or placebo for 16 weeks. PASI75 response rates in the experimental groups were 37.2%, 51.2%, 58.1%, 65.1% and 78.6%, respectively, compared to 9.3% in the placebo group. Additionally, the PASI90 response rates were 25.6%, 26.8%, 51.2%, 46.5% and 59.5%, compared to 2.3% in the placebo group, and PASI100 response rates were 11.6%, 9.8%, 25.6%, 23.3% and 40.5%, compared to 0% in the placebo group[86,87] Phase IIb (FRONTIER2): over 52 weeks, sustained high rates of skin clearance, particularly in 100 mg po bid, which saw PASI75 responses of 78.6% at 16 weeks and 76.2% at 52 weeks. Secondary end points, including PASI90, PASI100 and Investigator's Global Assessment scores, also showed consistent efficacy[88]	Phase IIb (FRONTIER1): most reported adverse effects were SARS-CoV-2 infection, nasopharyngitis and upper respiratory tract infection[87] Phase IIb (FRONTIER2): 58.6% of patients reporting adverse events such as nasopharyngitis, upper respiratory tract infections and COVID-19, without a dose-dependent increase in these events[88]	Phase III (ICONIC-LEAD): aims to evaluate the long-term (156 weeks) efficacy and safety in a significant group – 684 individuals with chronic plaque psoriasis. Expected to be completed in the future[89] Phase III (ICONIC-TOTAL): aims to evaluate 311 individuals with psoriatic plaques in specific regions – scalp, genital area, palms and soles. Expected to be completed in the future[90]

PASI, Psoriasis Area and Severity Index.

TNF inhibitors

TNF is a cytokine frequently involved in the pathogenesis of multiple inflammatory and autoimmune diseases. There are two biologically active forms of TNF: membrane-bound (mTNF) and soluble (sTNF), both of which assume trimeric configurations.[91] The receptors for this cytokine are TNFR1 and TNFR2.[92] TNFR1 is expressed in almost all cells of the body, activating the NF-κB and MAPK pathways, promoting a pro-inflammatory response. Thus, it is responsible for most of the biological effects of TNF, making it a common therapeutic target in these pathologies.[93] On the other hand, TNFR2, which only reacts to mTNF, is expressed only by immune, endothelial and glial cells, playing a more secondary role in the inflammatory process.[94]

In psoriasis, TNF amplifies the inflammatory process through various pathways: it recruits lymphocytes, facilitates their entry into tissues by inducing the expression of adhesion molecules in vascular endothelial cells, activates dermal dendritic cells and macrophages, and promotes the differentiation and proliferation of keratinocytes, leading to the formation of psoriatic plaques.[95]

Given the key role of TNF in the inflammatory process of psoriasis, multiple biological drugs (such as etanercept, adalimumab, certolizumab and infliximab) target this pathway, inhibiting both mTNF and sTNF.[3,96]

SAR441566

SAR441566, developed by the French pharmaceutical company Sanofi, is a small oral molecule aimed to promote the stabilization of asymmetric configurations of the sTNF trimer, preventing its binding to TNFR1 receptors, and consequently inhibiting the production of pro-inflammatory cytokines.[97,98]

In a phase I clinical trial published in 2023, 38 participants with moderate-to-severe plaque psoriasis were randomly distributed in a 2:1 ratio between an experimental group, which was administered SAR441566 twice daily, and a placebo group (Table 5). After 4 weeks, 58.3% of individuals in the experimental group showed improvement of one category or more in the Investigator's Global Assessment score, compared to 0% in the placebo group. No significant adverse effects were reported.[99,100]

Currently, a phase II clinical trial (SPECIFI-PSO) is underway to evaluate the efficacy and safety of SAR441566 (in five different doses) compared to placebo in treating ~200 individuals with moderate-to-severe psoriasis over 12 weeks (Table 5). The estimated completion date of the study is in the future.[101]

S1PR1 modulators

Sphingosine-1-phosphate (S1P) is a bioactive lipid that binds to five G protein-coupled receptors (S1PR1 to S1PR5) and mediates cellular functions such as proliferation, survival, migration and adhesion.[102] S1PR1 is particularly expressed by lymphocytes, playing an essential role in the migration of these cells from secondary lymphoid organs to tissues during the inflammatory process.[103] Modulators of this receptor are of great therapeutic interest in treating inflammatory diseases like psoriasis because they promote the internalization of S1PR1, preventing the binding of S1P to lymphocytes and blocking lymphocytic infiltration in inflamed areas.[104]

Vibozilimod

Vibozilimod (also known as SCD-044) is an oral S1PR1 immunomodulator in development by the Indian pharmaceutical company Sun Pharmaceutical Industries Limited, aimed at treating both psoriasis and atopic dermatitis.[105] According to Sun Pharma, it has demonstrated (in an undisclosed phase I clinical trial) efficacy in reducing lymphocyte counts in healthy individuals (Table 6).[105]

Currently, a phase II clinical trial (SOLARES-PsO-1) is underway to evaluate the efficacy and safety of vibozilimod (in three unspecified doses) compared to placebo in treating 240 participants with moderate-to-severe chronic plaque psoriasis (Table 6). The estimated completion date of the study is in the future.[106]

A3AR agonists

A3AR is a Gi protein-coupled receptor found on the surface of peripheral blood mononuclear cells.[107,108] In inflammatory diseases such as psoriasis, rheumatoid arthritis and Crohn's disease, there is an overexpression of this receptor. When activated, it mediates the inhibition of the NF-κB signalling pathway, reducing the expression of inflammatory cytokines like TNF, IL-12, IL-17 and IL-23, thus inducing an anti-inflammatory effect and inhibiting keratinocyte proliferation.[109,110]

Activating A3AR is a known and effective strategy in treating and managing immune-mediated inflammatory diseases, being the predominant mechanism of action of MTX.[111]

Piclidenoson

Piclidenoson (formerly designated CF101) is an oral A3AR agonist developed by the Israeli pharmaceutical company Can-Fite BioPharma.[2] In 2009, its efficacy and safety in treating moderate-to-severe plaque psoriasis were

Table 5. TNF inhibitor studies on efficacy and adverse effects of oral therapies in psoriasis.

Treatment	Mechanism of action	Efficacy	Adverse events	Future directions
SAR441566	TNF inhibitors	Phase I: 38 participants with psoriasis were randomly distributed in a 2:1 ratio between an experimental group, which was administered bid dose, and a placebo group. After 4 weeks, 58.3% of individuals in the experimental group showed improvement of one category or more in the Investigator Global Assessment score compared to 0% in the placebo group[99,100]	Phase I: no significant adverse effects were reported[100]	Phase II (SPECIFI-PSO): aims to evaluate the efficacy and safety of five different doses compared to placebo in treating about 200 individuals with moderate-to-severe psoriasis over 12 weeks. The estimated completion date of the study is in the future[101]

Table 6. S1PR1 modulator studies on efficacy and adverse effects of oral therapies in psoriasis.

Treatment	Mechanism of action	Efficacy
Vibozilimod (SCD-044)	S1PR1 agonist	Undisclosed phase I: efficacy in reducing lymphocyte counts in healthy individuals[105] Phase II (SOLARES-PsO-1): underway to evaluate the efficacy and safety in three unspecified doses compared to placebo in treating 240 participants with moderate-to-severe chronic plaque psoriasis. The estimated completion date of the study is in the future[106]

evaluated in a phase II clinical trial (Table 7). Seventy-six individuals with moderate-to-severe chronic plaque psoriasis were divided into three experimental groups, receiving piclidenoson in twice-daily doses of 1, 2 and 4 mg, and a placebo group.[112] After 12 weeks, the group receiving 2 mg had the highest PASI50 response rate at 35.3%, and mean change from baseline in the PASI score *versus* placebo throughout the study period was observed, with a statistically significant difference on weeks 8 and 12 (p=0.047 and p=0.031, respectively). The 1 and 4 mg groups showed similar rates to placebo.[113]

Subsequently, in 2015, a phase II/III trial was conducted with 293 participants with psoriasis divided into two groups, receiving twice-daily doses of 2 mg of piclidenoson or placebo (Table 7).[114] Although no significant differences were noted during the first 12 weeks, by week 32, 63.5%, 35.5%, 24.7% and 10.6% of patients in the experimental group had achieved PASI50, PASI75, PASI90 and PASI100 response rates, respectively. Piclidenoson was well tolerated, with no significant adverse effects reported.[115]

More recently, a phase III clinical trial was conducted with 528 participants with moderate-to-severe psoriasis, divided into four groups, receiving twice-daily doses of 2 and 3 mg of piclidenoson, 30 mg of apremilast (PDE4 inhibitor) or placebo (Table 7).[116] Although the initial results released in 2022 were promising, inconsistencies were reported by the FDA's quality control.[15]

In 2023, both the EMA and the FDA authorized new phase III clinical trials to investigate the potential use of piclidenoson in treating psoriasis.[2]

Oral microbials

In recent years, studies have suggested a link between systemic inflammatory diseases and the integrity of the gut microbiota.[117] One study even demonstrated that stool samples from individuals with psoriasis have lower gut microbiota diversity compared to a healthy control group, theorizing that gut dysbiosis may trigger a systemic inflammatory response that disrupts skin homeostasis.[2,118] Thus, oral microbial agents are currently under investigation and may become a promising therapeutic option for psoriasis.[2]

EDP1815

EDP1815 is a non-live pharmacological preparation of a strain of the bacterium *Prevotella histicola*, developed by the American biotechnology company Evelo Biosciences. Whilst it does not colonize or directly alter the gut microbiota, this agent interacts with innate immune cells in the small intestine, activating them and promoting their migration to mesenteric lymph nodes. There, they interact with T lymphocytes, inducing an anti-inflammatory response.[119]

In preclinical studies with murine models of T_H1-induced and T_H17-induced inflammation, EDP1815 demonstrated efficacy in reducing systemic inflammation (Table 8).[119] Subsequently, in a phase I clinical trial, individuals with psoriasis who were administered low-dose and high-dose EDP1815 demonstrated an average reduction in the Lesion Severity Score of 23% and 15%, respectively, after 4 weeks; in contrast, the placebo group showed a 1% increase. No significant adverse effects were reported (Table 8).[119]

More recently, in a phase II trial, 249 individuals with mild-to-moderate psoriasis were divided into three experimental groups, receiving daily doses of 1, 4 or 10 capsules (0.8×10^{11} cells in each capsule) of EDP1815 and a placebo group (Table 8). After 16 weeks, all experimental groups achieved PASI50 response rates (29.7%, 31.9% and 25.0%, respectively) that were significantly higher than in the placebo group (12.1%). In a 24-week follow-up, 60% of individuals who had achieved a PASI50 response at 16 weeks maintained it without recurrence or worsening of psoriasis. No significant adverse effects were reported.[2,120]

Currently, no new clinical trials are underway regarding the applicability of EDP1815 in treating psoriasis.[2]

KBL697

KBL697 is an oral probiotic developed by the South Korean biotechnology company KoBioLabs from a strain

Table 7. A3AR agonist studies on efficacy and adverse effects of oral therapies in psoriasis.

Treatment	Mechanism of action	Efficacy	Adverse events	Future directions
Piclidenoson (previously CF101)	A3AR agonists	Phase II: 26 individuals with moderate-to-severe chronic plaque psoriasis were divided into three experimental groups, receiving 1 mg po bid, 2 mg po bid and 4 mg po bid, and a placebo group. After 12 weeks, 2 mg po bid had the highest PASI50 response rate at 35.3%, and mean change from baseline in the PASI score *versus* placebo throughout the study period was observed, with a statistically significant difference on weeks 8 and 12 (p=0.047 and p=0.031, respectively). The 1 and 4 mg groups showed similar rates to the placebo[112,113] Phase II/III: conducted with 293 participants with psoriasis divided into two groups: 2 mg po bid or placebo. No significant differences were noted during the first 12 weeks. However, by week 32, 63.5%, 35.5%, 24.7% and 10.6% of patients in the experimental group had achieved PASI50, PASI75, PASI90 and PASI100 response rates, respectively[114,115] Phase III: conducted with 528 participants with moderate-to-severe psoriasis, divided into four groups: 2 mg po bid, 3 mg bid, 30 mg po bid apremilast or placebo. Although the initial results released in 2022 were promising, inconsistencies were reported by the FDA's quality control[15,116]	Phase II/III: no significant adverse effects reported[115]	In 2023, both the EMA and the FDA authorized new phase III clinical trials to investigate the potential use of piclidenoson in treating psoriasis[2]

PASI, Psoriasis Area and Severity Index.

of the bacterium *Lactobacillus gasseri*, which, unlike EDP1815, is a live agent, directly altering the gut microbiome.[121]

In 2020, a phase I clinical trial evaluating the safety and tolerability of KBL697 in 36 healthy participants was completed (Table 8).[122] More recently, in March 2024, a phase II trial was concluded to compare the efficacy and safety of low-dose and high-dose KBL697 in 80 individuals with plaque psoriasis (Table 8).[123] However, the results of both studies have not yet been disclosed.[2]

Discussion

In the current era, the development of small, orally administered molecules has become a priority in the search for therapies to treat psoriasis. The goal is to combine the efficacy of biologic drugs with more economically accessible and practical administration methods for patients affected by this pathology, whilst also avoiding potentially significant adverse effects.

Given the complex pathophysiology of psoriasis, there is a notable diversity of drugs under development, targeting specific pathways of this disease. Amongst JAK inhibitors (with recent emphasis on TYK2 inhibitors), following the FDA approval of deucravacitinib in 2022, zasocitinib stands out as it is currently being evaluated in two phase III clinical trials. Regarding PDE4 inhibitors, two drugs, orismilast and mufemilast, are also at a similar stage of study. JNJ-2113, an IL-23 inhibitor, after demonstrating promising results in phase II trials, has also progressed to phase III trials. Finally, piclidenoson, an A3AR agonist, has recently received approval for phase III clinical trials.

Table 8. Oral microbial therapy studies on efficacy and adverse effects of oral therapies in psoriasis.

Treatment	Mechanism of action	Efficacy	Adverse events	Future directions
EDP1815	*Prevotella histicola* bacterium	Animal Studies: in murine models of T helper 1-induced and T helper 17-induced inflammation, EDP1815 demonstrated efficacy in reducing systemic inflammation[119] Phase I: individuals with psoriasis who were administered low-dose and high-dose EDP1815 demonstrated an average reduction in the Lesion Severity Score of 23% and 15%, respectively, after 4 weeks; in contrast, the placebo group showed a 1% increase[119] Phase II: 249 individuals with mild-to-moderate psoriasis were divided into three experimental groups: receiving daily doses of 1, 4 or 10 capsules (0.8×10^{11} cells in each capsule) of EDP1815 and a placebo group. After 16 weeks, all experimental groups achieved PASI50 response rates (29.7%, 31.9% and 25.0%, respectively) significantly higher than the placebo group (12.1%). In a 24-week follow-up, 60% of individuals who had achieved a PASI50 response at 16 weeks maintained it without recurrence or worsening of psoriasis[2,120]	Phase I: no significant adverse effects were reported[119] Phase II: no significant adverse effects were reported[2,120]	No new clinical trials are underway for treating psoriasis[2]
KBL697	*Lactobacillus gasseri* bacterium	Phase I: evaluating the safety and tolerability in 36 healthy participants was completed. Results not yet disclosed[2,122] Phase II: the study compared the efficacy and safety of low-dose and high-dose KBL697 in 80 individuals with plaque psoriasis. Results not yet disclosed[2,123]		

PASI, Psoriasis Area and Severity Index.

The introduction of new small-molecule oral therapies like TYK2, PDE4 inhibitors and S1PR1 modulators has the potential to reshape the treatment landscape for psoriasis. These therapies offer a compelling alternative to biological drugs by precisely targeting pathways involved in the inflammatory process. Although they may not surpass biologics in terms of overall effectiveness, their ease of oral administration and symptom management make them valuable. This transition towards oral therapies could lead to more convenient treatment regimens for patients, enhancing adherence and improving their quality of life.

Despite their promise, the safety profiles of these new therapies pose some concerns. For example, PDE4 inhibitors like orismilast and mufemilast have demonstrated lower tolerability compared to existing biological treatments, with higher rates of adverse effects such as nausea, diarrhoea and headaches. Clinical trials have shown that these side-effects often lead to higher discontinuation rates, especially at higher doses. This underscores the importance of carefully managing these new treatments in clinical practice to ensure they provide a safe and effective alternative for patients with psoriasis.

Conclusion

The landscape of immune-mediated inflammatory diseases, including psoriasis, is rapidly changing with the development of these drugs. It is expected that, over the coming years, deucravacitinib and apremilast will lose their status as the only small, orally administered molecules used to treat psoriasis. However, the importance of conducting comprehensive, well-structured and long-duration clinical trials is emphasized to better understand the long-term efficacy, safety and tolerability of these agents.

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