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REVIEW

Biologics and small molecules for psoriasis: current and future progress

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Abstract

Advances in the understanding of the pathophysiology of psoriasis have led to the development of biologic therapies that target key components of the immune system involved in the inflammatory cascade of psoriasis, revolutionizing the management of moderate-to-severe cases. Alongside biologics, small molecules have emerged as promising treatment options. However, despite significant progress, several challenges remain. Additionally, long-term safety data for many newer agents are still lacking, necessitating ongoing surveillance and real-world evidence collection. This narrative review, performed by analysing the existing medical literature using PubMed, Ovid, Scopus, Embase and Cochrane Library databases up to 30 June 2025, explores new systemic therapies for psoriasis, including both approved and emerging biologics and small molecules, highlighting future directions in treatment. Despite advancements in psoriasis treatment, unmet needs persist, including specific clinical phenotypes such as pustular psoriasis, paradoxical reactions, patient comorbidities, treatment resistance or inefficacy, and high costs, underscoring the need for novel and emerging therapies. In the future, advances in pharmacogenetics and artificial intelligence could revolutionize psoriasis management. Artificial intelligence-driven models integrating clinical data, laboratory findings and biomarkers could enhance precision medicine by optimizing treatment selection and establishing standardized therapeutic algorithms, ensuring that patients receive the right drug at the right time.

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Introduction

Psoriasis is a chronic, immune-mediated inflammatory disorder that affects approximately up to 3% of the population worldwide.[1,2] The most common form, plaque psoriasis, is characterized by erythematous-desquamative plaques typically involving the scalp, elbows, knees and lower back.[3–5] The disease significantly impacts quality of life (QoL) and is associated with multiple comorbidities, including psoriatic arthritis (PsA), cardiovascular disease and depression.[6–9] Whilst its exact aetiology is still not understood, genetic susceptibility and environmental triggers seem to play a crucial role.[10,11]

The IL-17–IL-23 axis seems to play a central role in the pathogenesis of psoriasis by driving chronic inflammation and keratinocyte hyperproliferation.[12] Traditional treatments follow a stepwise approach, including topical agents, phototherapy and conventional systemic agents (e.g. methotrexate, cyclosporine and acitretin).[13,14] However, these systemic therapies may have limitations in terms of efficacy, tolerability and long-term safety, necessitating the development of more targeted and effective therapeutic options. Advances in our understanding of the pathophysiology of psoriasis have led to the emergence of biologic therapies targeting key components of the immune system involved in the inflammatory cascade of psoriasis, which have revolutionized the management of moderate-to-severe psoriasis.[13,14]

These therapies primarily inhibit pro-inflammatory cytokines such as tumour necrosis factor (TNF), IL-12–IL-23, IL-17 and IL-23.[15,16] Biologics, particularly the latest approved ones (anti-IL-17 and anti-IL-23), have significantly improved treatment outcomes, offering higher efficacy, durable responses and a favourable safety profile compared to conventional systemic therapies.[15,16]

In addition to biologics, small molecules, such as phosphodiesterase 4 (PDE4) inhibitor (apremilast) and tyrosine kinase 2 (TYK2) inhibitor (deucravacitinib), have emerged as promising treatment options for psoriasis.[15,16] Despite these advances, challenges remain: primary/secondary inefficacy, immunogenicity, paradoxical reactions, high costs and safety concerns still need to be addressed.[17–21] This review summarizes current and emerging systemic therapies for psoriasis, biologics and small molecules, with a focus on efficacy, safety and future perspectives.

Methods

A narrative review of the current literature was performed by analysing the existing medical literature using PubMed, Ovid, Scopus, Embase and Cochrane Library databases up to June 30, 2025. This review focuses on available data about both currently approved and emerging advanced systemic drugs for psoriasis. The search strategy incorporated specific research terms such as "psoriasis treatments", "guidelines", "biologics, "small molecules", "anti-TNF", "anti-IL-12/23", "anti-IL-23", "anti-IL-17", "clinical trial" and "real-life experiences". The search included all fields (title, abstract, keywords and full text). Moreover, references were examined to capture any potentially overlooked manuscripts. Herein, the main results from clinical trials evaluating the investigated drugs for psoriasis management were discussed. Regarding real-world evidence, only data from the most relevant studies, selected based on the number of patients and data accuracy, were included. Non-English language manuscripts were excluded from the analysis. It is important to note that the information presented in this article is based on data from previously conducted studies. Lastly, studies were selected based on clinical relevance and quality of data, irrespective of national origin. As a result, several references from Italian author groups were included, particularly when reporting large real-life cohorts or offering insights not covered by international trials.

This review is structured into two parts: the first part focuses on anti TNF and anti-IL-17 agents, whilst the second part covers anti-IL-23 drugs, small molecules and future directions.

Review

TNF inhibitors

Etanercept

Etanercept was the first biologic approved by the FDA for moderate-to-severe psoriasis in 2004. It is a fusion protein combining the TNF receptor with the Fc fragment of IgG1, which binds soluble and transmembrane TNF as well as lymphotoxin-α.[22] The recommended adult dose is 50 mg subcutaneously twice weekly for 12 weeks, followed by once weekly; in children aged ≥6 years, dosing is 0.8 mg/kg weekly (maximum 50 mg).[23]

Its efficacy has been demonstrated in multiple randomized controlled trials (RCTs). Eight trials consistently showed superiority of both high-dose (50 mg twice weekly) and low-dose regimens (50 mg weekly or 25 mg twice weekly) over placebo, with Psoriasis Area and Severity Index 75 (PASI75) response rates ranging from 40% to 59% and 30% to 45%, respectively.[24] Etanercept was also superior to acitretin.[24] In a post hoc analysis of 506 patients, responses were maintained up to 4 years.[25]

Real-life data further support etanercept effectiveness. In a 36-month multicentre study of 926 patients, both continuous and intermittent regimens improved efficacy and QoL by week 12; in the intermittent group, the mean drug-free interval was 12.9±12.8 weeks and retreatment restored responses.[26] The large phase IV OBSERVE-5 registry (2510 patients) confirmed long-term efficacy and safety: 22.2% experienced serious adverse events (SAEs), most commonly coronary artery disease (0.6%), osteoarthritis (0.6%), myocardial infarction (0.7%), cellulitis (0.9%) and pneumonia (1.2%). Fifty-five deaths were reported, with four considered potentially related to treatment. Malignancies occurred in 4.9% of patients, including non-melanoma skin cancer in 2.6%; lymphoma and tuberculosis were each reported in 0.1%.[27]

Regarding safety, long-term data confirm a favourable profile. In a post hoc analysis of 108 patients treated for 48 months, no cumulative toxicity was observed, and the rates of cardiovascular events, infections or malignancies did not increase over time.[25] The most frequent adverse events (AEs) were nasopharyngitis and upper respiratory tract infections (URTIs). Serious infections were rare, with only nine cases reported, including appendiceal abscess and septic shock.[25] Importantly, no reactivation of latent tuberculosis or opportunistic infections was observed. Across studies, the incidence of infections, malignancies and lymphoma was comparable to that expected with traditional systemic therapies such as methotrexate or cyclosporine.[27]

Infliximab

Infliximab is a chimeric IgG1 monoclonal antibody targeting soluble and transmembrane TNF, approved in 2006 for moderate-to-severe psoriasis. It is administered intravenously at 5 mg/kg at weeks 0, 2 and 6, then every 6–8 weeks.[28] Its efficacy was demonstrated in three pivotal RCTs, with rapid onset: PASI75 was achieved in 79% of patients by week 10, and responses were maintained at 6 and 12 months in 74% and 53%, respectively. Secondary loss of efficacy occurred in ~19%, associated with antidrug antibodies.[29–31] In a phase III trial of 835 patients, continuous therapy was superior to intermittent dosing, with PASI75 at week 50 of 44% (3 mg/kg) and 55% (5 mg/kg) in the continuous groups *versus* 25% and 38% with intermittent regimens.[31] Real-world evidence confirmed these findings. In the REALITY study (660 patients), 56.8% achieved PASI75 by week 50, and amongst early responders, 64.7% maintained PASI75 at week 50 and 66.3% at week 98. Patients naive to biologic therapy showed better outcomes than those previously treated.[32] In a retrospective series of 63 treatment courses, combination therapy prolonged drug survival, whereas obesity and infusion reactions predicted discontinuation; PASI75 responses at 24 and 52 weeks were consistent with RCTs, though 59% discontinued after a median of 12 months for loss of efficacy.[33] Regarding safety, pooled RCT data showed no cumulative toxicity after 12 months. Reported AEs included elevated liver enzymes (3–5%), lupus-like syndrome (2 cases) and infusion reactions (5 severe, 4 hypersensitivities within 14 days). Two cases of active tuberculosis were observed, highlighting the need for screening.[31,34,35] The REALITY study confirmed tolerability over 2 years: infusion reactions occurred in 7.7%, serious infections in 2.3% (including three tuberculosis and two cellulitis), whilst lymphoproliferative disorders and malignancies were seen in 0.6%. Discontinuations for AEs occurred in 13.7% of patients. Most events, such as nasopharyngitis, URTIs, headaches or joint pain, were mild. No cases of demyelinating disorders or worsening heart failure were reported.[32] The pattern of AEs aligned with previous data, confirming that long-term infliximab treatment for plaque psoriasis is well tolerated.[36]

Adalimumab

Adalimumab is a fully human IgG1 monoclonal antibody that binds soluble and membrane-bound TNF that was approved for plaque psoriasis in 2008 (FDA, later EMA).[37] The standard dosing is 80 mg s.c. initially, followed by 40 mg at week 1 and then every other week for adults, whereas in children aged ≥4 years, it is 0.8 mg/kg (max 40 mg) weekly for two doses, then every other week.[37] Its efficacy was first established in pivotal RCTs.[38–49] In the REVEAL study, PASI75 was achieved as early as week 4 and maintained with continued treatment; patients achieving PASI75 at week 16 showed a 92% improvement from baseline, sustained at 89% by week 33. Long-term extension confirmed maintenance of PASI75/90/100 over 3 years, with responses regained after retreatment.[38,45–48] The CHAMPION trial demonstrated superiority over methotrexate, with higher PASI75 and PASI90 rates independent of BMI.[39,42] Health-related QoL also improved significantly, as shown by Dermatology Life Quality Index (DLQI) and SF-36 scores.[43,44] The BELIEVE study tested adalimumab with or without topical calcipotriol/betamethasone; whilst topicals accelerated early response, by week 16, PASI75, PASI90 and PASI100 were not superior to adalimumab monotherapy.[49] Real-world data confirmed these findings. A single-centre retrospective study of 316 patients followed for 9 years showed rapid and sustained PASI responses even in older or biologic-experienced patients or those with obesity, consistent with trial data.[50] Long-term safety was extensively assessed in REVEAL and its extension: the AE rate was 3.99 per patient-year, with SAEs at 0.06 per patient-year, and no increased risk of serious infections, malignancies, demyelinating disorders, lupus-like syndrome or lymphoma.[38,45] The ESPRIT registry, a 10-year observational study including 6014 patients with 28,161 person-years of exposure, provided robust safety data. Serious infections occurred at 1.0/100 person-years, within the expected range for patients with psoriasis not on biologics (0.3–2.1). Malignancy incidence was 1.3/100 person-years, comparable to published rates (0.5–2.0).[51] Cardiovascular events were rare, with acute myocardial infarction at 0.1/100 person-years and stroke at 0.2/100 person-years, both lower than general psoriasis populations.[51] Importantly, >95% of patients remained free of serious infection or malignancy after 10 years. Injection-site reactions were uncommon (0.2/100 person-years), whilst tuberculosis, oral candidiasis, lupus-like reactions and demyelinating disorders each occurred at <0.1/100 person-years.[51] Mortality was also lower than expected: only 60 deaths occurred *versus* 144 predicted, corresponding to a standardized mortality ratio 58% below that of the matched general population.[51,52]

Certolizumab pegol

Certolizumab pegol is a PEGylated Fab fragment of a humanized IgG4 antibody that binds soluble and transmembrane TNF. Unlike other TNF inhibitors, it lacks an Fc portion, resulting in minimal placental and breastmilk transfer, which makes it particularly suitable in pregnancy and breastfeeding.[53–56] It was approved in Europe in 2020 for moderate-to-severe plaque psoriasis, administered s.c. at 400 mg at weeks 0, 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks; escalation to 400 mg biweekly may be considered in non-responders.[53,54] Efficacy was demonstrated in pivotal trials. In CIMPASI-1/2 and CIMPACT, both 200 mg and 400 mg biweekly achieved significantly higher PASI75 and Physician's Global Assessment score of 0 or 1 (PGA 0/1) responses *versus* placebo at week 16, with PASI90 and QoL improvements maintained up to 3 years.[55–60] In CIMPACT, certolizumab 400 mg biweekly

was superior to etanercept for PASI75 at week 12, whilst 200 mg biweekly was non-inferior.[55]

Real-world effectiveness has been confirmed in the CIM-REAL study, a large prospective non-interventional trial including 399 patients across Europe and Canada.[61] After 12 months, PASI75 and PASI90 were achieved by 77% and 56.5% of patients, respectively, whilst PASI ≤3 and ≤2 increased from 49.8% and 41.1% at 3 months to 82.0% and 75.3% at 12 months. QoL improved substantially, with mean DLQI decreasing from 12.4 to 2.3 and DLQI 0/1 rising from 28.6% to 59.4%. Treatment persistence at 1 year was ~85%. In an Italian real-life cohort (*n*=153), certolizumab significantly reduced PASI and improved nail and joint symptoms as early as week 12, with sustained benefits up to week 52.[62]

Safety across trials and real-world studies was favourable. In CIMPASI/CIMPACT, infections, injection-site reactions and skin disorders were the most frequent AEs, mostly mild; SAEs occurred in 3.5% of certolizumab patients *versus* 3.7% on placebo, with discontinuation rates of ~1.5%.[55,57] Long-term pooled data up to 144 weeks showed an SAE incidence of 7.5/100 patient-years without cumulative risk; malignancies were rare (1.4%), serious cardiovascular events occurred at 0.4/100 patient-years, and tuberculosis was reported in one case.[63] Oral candidiasis, lupus-like reactions or demyelinating disorders were very uncommon; two cases of multiple sclerosis were reported amongst nearly 1000 patient-years of exposure.[63]

Anti-IL-17

Secukinumab

Secukinumab is a fully human IgG1/κ monoclonal antibody that selectively neutralizes IL-17A. Approved in 2015, it was the first IL-17A inhibitor indicated for moderate-to-severe psoriasis in adults, adolescents and children aged ≥6 years.[64–71] It is given s.c. at 300 mg in adults, or weight-based dosing in children, with induction at weeks 0–4 followed by monthly maintenance.[71] In patients ≥90 kg, biweekly dosing may be more effective.[72]

Its efficacy was demonstrated in pivotal phase III trials. In ERASURE (*n*=738) and FIXTURE (*n*=1306), secukinumab 300 mg and 150 mg achieved significantly higher PASI75 and PASI90 responses *versus* placebo and etanercept.[72,73] In FIXTURE, superiority over etanercept was sustained up to 52 weeks.[73] Long-term efficacy was confirmed in the SCULPTURE extension: PASI75/90/100 responses at year 1 (88.9%, 68.5%, 43.8%) were maintained through year 5 (88.5%, 66.4%, 41%), with mean PASI improvement of ~90% and DLQI 0/1 in 65.5%.[74] In the CLEAR study, secukinumab was superior to ustekinumab at week 16 for PASI90 and PASI100.[67,70] Secukinumab also proved effective in psoriatic arthritis and difficult-to-treat sites such as nails, scalp, palms and soles.[75–78]

Real-world studies confirmed its effectiveness and safety.[79–83] Responses appear higher in bio-naive patients[79,80] but secukinumab is also effective in patients previously exposed to anti TNF therapy or in those in whom it failed.[84,85] Registry and observational data support its use in older patients[86] and in those with prior malignancy.[87]

The safety profile is favourable and consistent with trials. Common AEs include nasopharyngitis, URTIs, headache, diarrhoea and arthralgia.[73,88] Oral candidiasis occurs but less frequently than with brodalumab or bimekizumab.[89] Inflammatory bowel disease (IBD) has been reported but appears uncommon; a pooled analyses of >3900 patients found no causal link.[90,91] Rare events include eczematous eruptions, vasculitis and lupus-like reactions.[88] Long-term data up to 5 years confirmed no unexpected safety signals and stable rates of infections, malignancies and cardiovascular events.[88,92]

Ixekizumab

Ixekizumab is a humanized IgG4 monoclonal antibody targeting IL-17A, blocking its binding to the receptor and downstream keratinocyte activation.[93–95] It is approved for adults, adolescents and children aged ≥6 years (≥25 kg) with moderate-to-severe psoriasis.[93–96] The recommended adult dose is 160 mg s.c. at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10 and 12, then 80 mg every 4 weeks.[93,94] Pivotal phase III trials (UNCOVER-1/2/3) demonstrated rapid and significant responses: at week 12, PASI75 was achieved in 88.7% (every 2 weeks) and 81.6% (every 4 weeks) *versus* 4.4% placebo, whilst static PGA (sPGA) 0/1 was reached in 81.8%, 75.0% and 3.9%, respectively.[97,98] Ixekizumab also achieved higher PASI90/100 rates than placebo and outperformed etanercept at week 12.[97,98] Long-term extensions confirmed sustained efficacy and safety over 5 years.[99–101] In paediatrics, IXORA-PEDS confirmed durable efficacy and safety up to 108 weeks.[101,102]

Head-to-head trials have positioned ixekizumab amongst the most effective IL-17 inhibitors. IXORA-R showed faster onset and superior clearance at week 12 *versus* guselkumab,[103] whilst IXORA-S demonstrated greater skin and nail efficacy *versus* ustekinumab at 1 year.[104] Ixekizumab is particularly effective on difficult-to-treat sites such as nails, scalp and palmoplantar psoriasis.[105–109] Case reports suggest lower relapse rates than secukinumab in erythrodermic psoriasis.[110–113] Real-world data corroborate trial findings. In a multicentre study of 638 patients, ixekizumab outperformed secukinumab in PASI100, PASI<3 and PASI90 at weeks 12, 24 and 48, with superior DLQI improvements.[114–117] No significant differences emerged *versus* brodalumab, though both agents showed high PASI90/100 responses.[117,118]

Safety data are consistent with the IL-17 inhibitor class. Common AEs include injection-site reactions, nasopharyngitis and mild infections; less frequent are neutropenia, fungal infections and antidrug antibody development. Rare events (<1%) include IBD onset, candidiasis and hypersensitivity reactions.[93]

Brodalumab

Brodalumab is a fully human IgG2 monoclonal antibody targeting the IL-17 receptor A (IL-17RA), thereby blocking multiple IL-17 cytokines (IL-17A, IL-17F, IL-17A/F, IL-17C, IL-17E).[119–121] This broad inhibition translates into a profound molecular response, with >95% suppression of psoriatic gene expression after 12 weeks.[121] It is FDA-approved for adults with moderate-to-severe plaque psoriasis unresponsive to other systemic therapies, at 210 mg s.c. at weeks 0, 1 and 2, then every 2 weeks.[121,122]

The AMAGINE-1/2/3 phase III trials established its high efficacy, with PASI75 achieved in up to 86% *versus* 8% with placebo ($p<0.001$) and rapid onset of complete or near-complete clearance.[121,123–125] Benefits were sustained up to 120 weeks.[124] Brodalumab was also effective in scalp[126] and nail psoriasis;[127] in the AMVISION-1/2 trials, it improved both skin and joint outcomes in psoriatic arthritis.[128,129] In a Japanese phase III trial, it was beneficial in generalized pustular and erythrodermic psoriasis, with most patients achieving remission or improvement at week 52.[130]

Real-life studies further confirmed its effectiveness and safety across diverse populations.[131–135] Brodalumab showed high rates of rapid PASI90/100 responses, including in difficult-to-treat sites, and maintained favourable drug survival.

The safety profile is consistent with IL-17 blockade: the most common AEs are nasopharyngitis, URTIs, Candida infections, headache and arthralgia.[121,122] Transient neutropenia was observed without severe infections. Although cases of suicide were reported during trials, no causal link was demonstrated; nonetheless, caution is advised in patients with depression or suicidal ideation.[120] Unlike other IL-17 inhibitors, brodalumab has not shown a clear signal for IBD flares but vigilance remains warranted.

Bimekizumab

Bimekizumab is a humanized IgG1 monoclonal antibody neutralizing both IL-17A and IL-17F, approved in June 2023 for adults with moderate-to-severe plaque psoriasis. The recommended dose is 320 mg (two s.c. injections of 160 mg) at weeks 0, 4, 8, 12 and 16, followed by every 8 weeks; in patients ≥120 kg with suboptimal response, maintenance every 4 weeks may be considered.[136–138]

Dual IL-17A/F blockade provides stronger suppression of inflammatory pathways than IL-17A inhibition alone.[139]

In BE ABLE 1, bimekizumab achieved a dose-dependent PASI90 response at week 12, significantly higher than placebo.[140] BE ABLE 2 confirmed long-term efficacy through week 60, with serious treatment-emergent AEs in 6.9%.[141] In the phase III BE READY trial, PASI90 and Investigator Global Assessment (IGA) 0/1 were reached at week 16 by 91.0% and 93.0% of patients, compared to 1.0% with placebo ($p<0.0001$ for both); PASI100 was achieved in 68.0%.[142]

Head-to-head studies demonstrated superiority of bimekizumab over other biologics. In BE VIVID, PASI90 and IGA 0/1 at week 16 were achieved by 85.0% and 84.0% of bimekizumab-treated patients *versus* 50.0% and 53.0% with ustekinumab and 5.0% and 5.0% with placebo ($p<0.0001$ for both comparisons).[143] In BE RADIANT, PASI100 at week 48 was achieved in 61.7% of patients on bimekizumab *versus* 48.9% on secukinumab ($p=0.006$), with sustained responses through week 96: PASI100 was maintained in 70.8% of patients continuing bimekizumab, whilst 76.6% of those switched from secukinumab achieved PASI100.[144,145] In BE SURE, PASI90 at week 16 was achieved in 86.2% of patients on bimekizumab compared with 47.2% on adalimumab ($p<0.001$), whilst IGA 0/1 was reached by 85.3% *versus* 57.2%, respectively ($p<0.001$).[146]

Pooled safety data from BE VIVID, BE READY, BE SURE and the extension BE BRIGHT identified nasopharyngitis, URTIs and oral candidiasis as the most frequent AEs. Over 3 years, candidiasis events were almost all mild or moderate (99.3%), discontinuations due to candidiasis were rare (1.5%), and incidence was lower with maintenance every 8 weeks than every 4 weeks.[139,147]

Real-world experiences confirm the effectiveness and tolerability of bimekizumab in the short and long term, with comparable responses and safety with respect to clinical trials, regardless of previous exposure to biologics.[148–150] Real-life data also suggest bimekizumab as a valuable treatment option for difficult-to-treat areas in patients with psoriasis.[148–153]

Anti-IL12/23

Ustekinumab

Ustekinumab is a human IgG1κ monoclonal antibody that binds the p40 subunit shared by IL-12 and IL-23. Ustekinumab involves subcutaneous administration in weeks 0 and 4 and every 12 weeks thereafter, at a dose that depends on the patient's age and weight. In adult patients, the dose is 45 mg for body weight <100 kg or 90 mg for body weight ≥100 kg. For children aged ≥12 years, the same adult schedule applies, except for those

with body weight <60 kg, who receive 0.75 mg/kg.[154] This drug was approved in 2009 for the treatment of moderate-to-severe plaque psoriasis.[155]

The PHOENIX 1 and 2 phase III, double-blind, placebo-controlled trials demonstrated its efficacy and safety. In PHOENIX 1, PASI75 was achieved in 67.1% and 66.4% of patients receiving ustekinumab 45 mg and 90 mg, respectively *versus* 3% treated with placebo at week 12.[156] PHOENIX 2 showed similar results, with PASI75 reached in 66.7% and 75.7% of patients receiving 45 mg and 90 mg, respectively, *versus* 3.7% with placebo.[157] AEs were comparable across groups and mostly mild (PHOENIX 1: 57.6%, 51.4% and 48.2% of patients receiving 45 mg and 90 mg of the drug and placebo, respectively; PHOENIX 2: 53.1%, 47.9% and 49.8% of patients receiving 45 mg and 90 mg of the drug and placebo, respectively). SAEs were rare and occurred at rates similar to placebo. Five-year follow-up of PHOENIX 1 showed that PASI75 was reached in 63.4% (45 mg) and 72% (90 mg) of patients, and PASI90 in 39.7% and 49%, respectively; safety remained stable over time.[158] In PHOENIX 2, PASI75 at week 244 was achieved in 76.5% (45 mg) and 78.6% (90 mg) of patients, and PASI90 in 50% and 55.5%, respectively.[159] Regarding safety, the data were comparable between the two groups, with no reported cases of tuberculosis activation.[159]

Over the past decade, numerous real-world studies have confirmed the effectiveness and safety of ustekinumab. An Italian 8-year study of nearly 400 patients reported PASI75, PASI90 and PASI100 rates of 76.2%, 61.9% and 57.1%, respectively, highlighting the durability of response.[160] Similar long-term results were reported in Turkish cohorts, with PASI ≤3 achieved in 80% of patients after 5 years, particularly amongst biologic-naive patients.[161,162] Data from China provided additional insights: one study showed that responses at week 4 could be negatively influenced by metabolic comorbidities,[163] whilst another demonstrated superiority of ustekinumab over TNF inhibitors at 6 months.[164] Real-life experience has also confirmed its role in difficult clinical settings. Pinheiro et al. showed meaningful responses in patients who had failed TNF inhibitors, with PASI75 achieved in 67.1%.[165] Damiani et al. extended these observations, reporting that ustekinumab remained effective even in patients who had failed both secukinumab and a TNF inhibitor.[166] Beyond skin clearance, improvements in QoL have been consistently observed, as highlighted by Hesselvig et al., who demonstrated significant DLQI improvement, particularly during the first months of treatment.[167]

Anti-IL-23

Guselkumab

Guselkumab is a human IgG1λ monoclonal antibody directed against the p19 subunit of IL-23, approved in 2017 for adults with moderate-to-severe psoriasis at a dose of 100 mg subcutaneously at weeks 0 and 4, followed by every 8 weeks.[168] In pivotal phase III trials, including VOYAGE 1 and VOYAGE 2, guselkumab demonstrated superior efficacy compared with placebo and adalimumab, with PASI90 responses in 70–73% of patients at week 16 and IGA 0/1 in more than 80% of patients.[169,170] Importantly, maintenance therapy preserved efficacy in the majority of responders, and patients who switched from adalimumab or ustekinumab achieved significant improvements when moved to guselkumab, as confirmed in the NAVIGATE study.[171] In the head-to-head ECLIPSE trial, guselkumab was superior to secukinumab for PASI90 at week 48, with similar safety outcomes.[172] Overall, clinical trials consistently confirmed both efficacy and a favourable safety profile.

Since real-world evidence has reinforced these findings, showing that guselkumab maintains high levels of skin clearance and good tolerability in daily practice. In a multicentre Italian cohort of 112 patients with prior inadequate response to ustekinumab, the proportion achieving PASI75, PASI90 and PASI100 progressively increased during follow-up, reaching 97.1%, 79.4% and 67.6% at week 104.[173] Similar long-term improvements were observed in a 104-week retrospective study, where PASI90 and PASI100 rose from 49% and 32.4% at week 16 to 79.6% and 61.1% at 2 years, without new safety signals.[174] Another Italian real-life experience documented marked PASI and body surface area (BSA) reductions over 44 weeks, with only one discontinuation due to liver enzyme elevation.[175] The PERSIST study confirmed the beneficial impact of guselkumab on QoL, with more than half of patients reaching DLQI ≤1 at week 28.[176]

Evidence from other countries has been consistent. In a Chinese cohort, 88.6% of patients achieved PASI90 and nearly half reached PASI100 at week 16, with no SAEs.[177] Long-term data over 148 weeks indicated lower PASI100 rates in patients with obesity and bio-experienced patients compared with those without obesity or who were bio-naive,[178] although other studies did not confirm a significant influence of BMI, smoking or comorbidities.[179] Importantly, guselkumab has shown strong efficacy in difficult-to-treat sites. In a prospective study, facial and genital psoriasis improved markedly, with sPGA 0/1 achieved in more than 75% of patients by week 12.[180] Nail psoriasis also responded, with significant reductions in Nail Psoriasis Severity Index scores observed from week 28 onwards.[181] Similarly, patients with scalp and palmoplantar involvement experienced meaningful improvements, even after failure of previous anti-IL-17 therapy.[182]

Risankizumab

Risankizumab is a humanized IgG1 monoclonal antibody targeting the IL-23p19 subunit, approved by the FDA and

EMA in 2019 for moderate-to-severe psoriasis at the dose of 150 mg subcutaneously at weeks 0 and 4 and then every 12 weeks.[183] In the pivotal phase III trials UltIMMa-1 and UltIMMa-2, risankizumab demonstrated clear superiority over ustekinumab and placebo, with PASI90 achieved in ~75% of patients and sPGA 0/1 in over 80% at week 16.[184] Similar results emerged in head-to-head studies against other biologics: in IMMvent, risankizumab outperformed adalimumab (PASI90 72% *versus* 47%),[185] whilst in IMMerge it was non-inferior to secukinumab at week 16 and superior at week 52, with PASI90 rates of 86.6% *versus* 57.1%.[186] Long-term data from the LIMMitless extension confirmed sustained responses, with more than 80% of patients maintaining PASI90 after 5 years with a low incidence of AEs.[187]

Beyond clinical trials, a large body of real-world evidence has confirmed both the efficacy and safety of risankizumab. In Italy, Megna et al. reported a rapid reduction of mean PASI from 12.3 at baseline to 2.7 at week 16,[188] whilst a multicentre study by Gargiulo et al. showed PASI75, PASI90 and PASI100 rates of 93.9%, 78.6% and 61.1% at 52 weeks, without relevant AEs.[189] Similar findings were observed in Poland and the Czech Republic, where PASI90 and PASI100 rates continued to increase up to week 52, achieved in more than 80% and 65% of patients, respectively.[190,191] Other studies have highlighted potential predictors of response: Borroni et al. found that high BMI and multiple biologic failures reduced the likelihood of achieving PASI90,[192] whereas other real-life cohorts, including Turkish and Italian studies, reported no significant impact of prior biologic exposure.[193,194]

The benefit of risankizumab has also been confirmed in difficult-to-treat sites. The VESPA study demonstrated consistent improvements not only in PASI and DLQI but also in scalp, nail, palmoplantar and genital involvement.[195] Bardazzi et al. noted that clearance of leg lesions may occur more slowly than global PASI improvement.[196] Importantly, risankizumab has proven effective in patients in whom previous TNF or IL-17 inhibitor therapy failed, with significant improvements in PASI and BSA even in heavily pre-treated populations.[197,198] Long-term observational evidence is also robust: the large IL-PSO study, including more than 1000 patients followed for 3 years, showed PASI improvements approaching 99% and PGA 0/1 achieved in over 75% of patients with difficult-to-treat sites after 1 year, with no unexpected safety signals.[199]

Tildrakizumab

Tildrakizumab is a humanized anti-IL-23p19 IgG1κ antibody approved for moderate-to-severe psoriasis, administered s.c. 100 mg at weeks 0 and 4, then every 12 weeks; escalation to 200 mg is possible in patients with high disease burden or >90 kg.[200,201]

In reSURFACE 1 (*n*=772), PASI75 at week 12 was achieved by 62% and 64% of patients receiving tildrakizumab 200 mg and 100 mg, respectively, compared to 6% with placebo. PGA 0/1 was achieved in 59%, 58% and 7%, respectively.[202,203] In reSURFACE 2 (*n*=1090), PASI75 at week 12 was achieved by 66% (200 mg), 61% (100 mg), 48% (etanercept) and 6% (placebo), whilst PGA 0/1 responses were 59% (both tildrakizumab doses), 48% (etanercept) and 4% (placebo).[202] AE and discontinuation rates were comparable across all treatment groups in both trials. Egeberg et al. presented a pooled analysis of the 5-year long-term extension of these two trials, confirming the safety of this drug.[204]

Real-life studies corroborate trial results. Ruggiero et al. reported PASI90 and PASI100 at week 28 in 76.1% and 61.9% of patients, sustained to week 52.[205] A Spanish study (*n*=190) showed an 88.8% PASI reduction and DLQI drop from 12.5 to 1.2 at 24 weeks.[206] The multicentre TILOT study (*n*=412) found PASI <5 in 88.4% of patients at week 52, with significant improvement also at scalp and nail sites.[207] Other studies confirmed efficacy in difficult areas (scalp, nails, palmoplantar and genital).[208–210] Wei et al. reported PASI reduction from 15.8 to 1.5 after 1 year.[211] Effectiveness was maintained in patients failing biologics, including anti-IL-17 or TNF agents.[212,213] Dose flexibility is supported by data: in patients with obesity, 200 mg was associated with higher PASI responses.[214,215] Safety in real-life was favourable, with only mild infections (nasopharyngitis, URTI) as the most common AEs.[216,217] The ESTER study confirmed safety and efficacy in older patients (mean age 73), with only mild events.[218] Other cohorts also demonstrated significant QoL improvements.[219–223]

Small molecules

Apremilast

Apremilast is an oral PDE4 inhibitor that modulates inflammatory pathways involved in psoriasis. It is titrated up to 30 mg twice daily in adults and in children ≥6 years weighing >50 kg, whilst a lower dose of 20 mg BID is recommended for those between 20 and 50 kg.[224] Its efficacy was established in the ESTEEM 1 and 2 trials, where PASI75 responses at week 16 were achieved in 28–33% of patients *versus* 5–6% with placebo, with significant improvements in DLQI.[225,226] These results were confirmed in a third phase III trial[227] as well as in the EMBRACE and DISCREET studies, which demonstrated benefits in difficult-to-treat areas and genital psoriasis.[228,229] Paediatric efficacy was confirmed in the SPROUT trial, with superior sPGA and PASI responses *versus* placebo and good tolerability.[230] Across trials, AEs were mostly mild gastrointestinal or respiratory events, with discontinuation rates of ~8%.[225]

Real-world studies have provided further support for apremilast effectiveness, particularly in patients

unsuitable for treatment with biologics. The OTELO study demonstrated clinically meaningful improvements, with PASI75 achieved in 35.1% of patients at 6 months and significant benefits in patient-reported outcomes.[231] An Italian multicentre cohort showed that PASI50 was obtained in 68% of patients within 4 months, with progressive gains up to month 36, including PASI90 in almost one-third.[232] Another Italian study reported marked improvements in PASI, BSA and DLQI over 1 year, with only 10.6% discontinuing for lack of efficacy.[233] The multinational APPRECIATE study confirmed reductions in PASI, BSA and DLQI over 6 months,[234] whilst van den Reek et al. showed significant improvements in QoL and work productivity sustained at 12 months.[235] Importantly, apremilast remains a therapeutic option in patients with prior malignancy, as shown by Podevin et al., although, in this setting, a higher discontinuation rate was observed due to gastrointestinal AEs.[236]

Deucravacitinib

Deucravacitinib is an oral selective TYK2 inhibitor approved for the treatment of moderate-to-severe plaque psoriasis in adults eligible for systemic therapy.[237] TYK2 is a member of the JAK family involved in the JAK–STAT signalling pathway, crucial in inflammatory processes such as psoriasis.[237] It is well established that TYK2 pairs with JAK2 for the signalling of IL-12 and IL-23, and it also pairs with JAK1 for signalling downstream of type I interferon receptors. On this basis, the therapeutic role of TYK2 inhibition has emerged in treating psoriasis.[238] Deucravacitinib, the first-in-class, allosteric TYK2 inhibitor approved for psoriasis, is administered at a dose of 6 mg once daily. Its efficacy and safety were demonstrated in two pivotal phase III, randomized, double-blind, placebo-controlled and apremilast-controlled trials: POETYK PSO-1 and POETYK PSO-2.[239] Of the 667 patients enrolled, 332 were randomized to receive deucravacitinib 6 mg OD, 168 were receiving apremilast 30 mg twice daily and 166 were in the placebo group. At week 16, PASI75 was achieved in 58.4% of patients receiving deucravacitinib compared with 35.1% on apremilast and 12.7% on placebo. Similarly, sPGA 0/1 was reached in 53.6%, 32.1% and 7.2%, respectively. Higher response rates were also observed for PASI90 (35.5%) and PASI100 (14.2%) compared to the other arms (apremilast PASI90/100: 19.6%/3%; placebo PASI90/100: 4.2%/0.6%).[239] Patients initially treated with placebo or apremilast and later switched to deucravacitinib (at week 16 if PASI50 was not achieved) showed similar long-term responses, with PASI75 achieved in 65.1% and 68.3% at week 52, respectively. Deucravacitinib also led to greater improvements in QoL, with DLQI 0/1 achieved in 41% at week 16 (*versus* 28.6% apremilast and 10.6% placebo). Scalp-specific PGA 0/1 was reached in 70.3% *versus* 39.1% and 17.4% in the same arms.[239] The study also evaluated the effects of deucravacitinib on safety, finding that the rate of AEs was comparable between the three groups. Specifically, AEs were detected in 53% of patients on deucravacitinib but only 2.1% were sAEs and a total of 1.8% of patients discontinued the drug due to AEs.[239] The most common AEs were nasopharyngitis (6.3%), URTIs (6.3%), headache (4.8%) and diarrhoea (3.9%).[239] Imafuku et al. formed a subgroup analysis of Japanese patients enrolled in POETYK PSO-1 and found data consistent with those already described on both the efficacy and safety of deucravacitinib.[240]

POETYK PSO-2, which enrolled 1020 patients, confirmed these findings. At week 16, PASI75 was achieved in 53% (deucravacitinib), 39.8% (apremilast) and 9.5% (placebo) of patients and sPGA 0/1 was achieved in 49.5%, 33.9% and 8.6% of patients, respectively.[241] Amongst PASI75 responders, rerandomization showed sustained benefit in 80.4% of patients continuing therapy *versus* 31.3% after switch to placebo.[241] The incidence of sAEs remained low (1.6%).[240] Further confirmation came from POETYK PSO-3 (PASI75 at week 16: 68.8% *versus* 8.1% in placebo; sPGA 0/1: 55.6% *versus* 6.8% in placebo)[242] and POETYK PSO-4, which included patients with erythrodermic and generalized pustular psoriasis, showing improvement in DLQI and symptoms.[243]

The long-term extension POETYK PSO-LTE reported sustained responses at week 148 (PASI75: 73.2%; PASI90: 48.1%; sPGA 0/1: 54.1%), with no new safety signals.[244] Moreover, 4-year safety and efficacy results from the phase III POETYK PSO-1, PSO-2 and long-term extension trials demonstrated a consistent safety profile and durable efficacy of deucravacitinib in patients with moderate-to-severe plaque psoriasis even over longer periods of treatment, including difficult-to-treat areas as scalp and fingernails.[245] Results from the pooled analysis of the POETYK PSO-1 and PSO-2 trials, as reported by Merola et al., indicated that deucravacitinib not only improved skin manifestations in patients with psoriasis but also significantly reduced joint pain and musculoskeletal symptoms in those who screened positive for PsA.[246] Since deucravacitinib was approved in 2024, few real-life data on it are still available. A 52-week study of 104 patients also evaluated the effectiveness of deucravacitinib on psoriasis of difficult-to-treat sites such as scalp, nails and genitalia.[247] At week 52, PASI75, PASI90 and PASI100 were obtained in 86.0%, 62.8% and 25.6% of patients, respectively. The regional PGAs of the indicated sites and DLQI were also reduced, with no serious or lethal AEs reported.[247] In a study of 33 patients, Hagino et al. also observed that deucravacitinib rapidly reduced pruritus as early as following 2 weeks of therapy, and at week 16 DLQI 0/1 was achieved by 42.9% of patients.[248] A case series by Tran et al. reported high discontinuation rates of therapy with deucravacitinib following acneiform eruptions, highlighting the importance of identifying patients at risk and of prevention or early treatment.[249]

A prospective, single-centre study by Hagino et al.[250] evaluated the effectiveness of deucravacitinib in patients with psoriasis, stratified by a history of apremilast or biologic usage. Previous use of apremilast does not appear to attenuate the clinical outcomes of treatment with deucravacitinib as previously observed in phase III clinical trials.[239–241] The rates of PASI75, PASI100 or absolute PASI ≤1 at week 52 in biologic-naive patients (84.4%, 24.4% or 53.3%) were slightly higher than those in biologic-experienced patients (57.1%, 14.3% or 28.6%), respectively. Globally, deucravacitinib proved a sustained 52-week effectiveness in different patient subgroups.[250] Moreover, a recent report on off-label use of deucravacitinib in cases of overlapping psoriasis and atopic dermatitis refractory to conventional medical management highlighted its successful use in this type of complex disease.[251]

New emerging drugs

Emerging therapeutic agents for psoriasis, including their targets, key drugs under investigation, efficacy outcomes, safety profile and stage of clinical development, are summarized in Table 1.

RORγt inhibitors

Retinoic acid receptor-related orphan receptor-γt (RORγt), a transcription factor essential for the differentiation of T helper 17 (T_H17) cells, is overexpressed and plays a critical role in the occurrence of several inflammatory and autoimmune diseases, including psoriasis. Several inhibitors that specifically target RORγt have been discovered and may represent promising drugs by inhibition of RORγt through ligand domain binding.[252,253]

Table 1. Summary of main emerging therapeutic agents for psoriasis, including their targets, key drugs under investigation, efficacy outcomes, safety profile and stage of clinical development.

Drug/class	Target/mechanism	Key agents	Efficacy summary	Safety	Development stage
RORγt inhibitors	Inhibition of RORγt, a transcription factor essential for T helper 17 cell differentiation	Vimirogant, retezorogant, bevurogant	PASI reduction up to 38% (PASI75 in 42% for retezorogant); IL-17A/F reduction	Headache, nausea, flushing, transaminase elevation	Phase II
ROCK2 inhibitors	Inhibition of ROCK2, reducing IL-23 and IL-17 cytokine production	KD025 (belumosudil)	PASI50 in 46% at 12 weeks (KD025); benefit seen with lower dose regimens	Reversible liver enzyme elevations in seven patients	Phase II
Other IL-23 inhibitors	IL-23p19 inhibition (mirikizumab, IBI112, icotrokinra)	Mirikizumab, IBI112, icotrokinra	PASI90 up to 86% (mirikizumab)	Generally well-tolerated; rare cardiovascular AEs with mirikizumab	Phase III (mirikizumab, development discontinued); icotrokinra (phase III); early phase (IBI112)
IL-36R inhibitors	IL-36 receptor inhibition (spesolimab, imsidolimab)	Spesolimab, imsidolimab	GPPGA pustulation score = 0 in 54% (spesolimab); rapid effect in generalized pustular psoriasis	No serious AEs with Imsidolimab; mild infections with spesolimab	Approved (spesolimab); phase III (imsidolimab)
JAK inhibitors	Inhibition of JAK–TYK2 pathway (e.g. zasocitinib, VTX958, tofacitinib, upadacitinib)	Zasocitinib, VTX958, tofacitinib, upadacitinib	PASI75 up to 68% (zasocitinib), 67% (VTX958); JAK inhibitor (e.g. upadacitinib) effective in PsA and eczematous psoriasis	Mostly mild/moderate AEs; long-term safety concerns for tofacitinib	Phase II–III (zasocitinib, VTX958); off-label/approved for PsA (others)

AEs, adverse events; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; ROCK2, Rho-associated protein kinase 2; RORγt, retinoic acid receptor-related orphan receptor γt.

Vimirogant (VTP-43742), an oral inhibitor of the RORγt protein, was compared to placebo in a phase II trial and demonstrated reductions of 29% and 23% in PASI score after 4 weeks in patients taking 700 mg and 350 mg of the drug, respectively. A significant decrease in levels of IL-17A and IL-17F was also observed.[254] AEs reported included headache, flushing, nausea and transaminase elevation. Retezorogant (JTE-451) was studied in a population of 152 patients in a placebo-controlled phase II trial (IMPACT-PS). After 4 weeks, an average PASI reduction of 30% and 38% was observed in patients administered 200 mg twice daily, and 33% and 42% of patients administered 400 mg twice daily achieved PASI75; a reduction in PASI was observed in only 17% of the patients in the placebo group.[255] Furthermore, the percentage of patients achieving PGA 0/1 was 25%, 28% and 9%, respectively. Another oral RORγt inhibitor, bevurogant was assessed in a randomized, double-blinded phase II study, with oral administration of 25, 50, 100 or 200 mg resulting in PASI75 in 5%, 7.7%, 10.3% and 30% of patients, respectively.[255]

ROCK2 inhibitors

Rho-associated protein kinase 2 (ROCK2) inhibitors have emerged as potential candidates for psoriasis treatment by reducing the production of pro-inflammatory cytokines and downregulating the T_H17 cell-driven autoimmune response. The phase II study by Zanin-Zhorov et al.[256] demonstrated that oral administration of a specific ROCK2 inhibitor, KD025, lead to PASI50 in 46% of patients with psoriasis vulgaris. Reduced levels of IL-23 and IL-17 were also found, whilst IL-6 and TNF levels remained unchanged. Clinical benefit, defined as any decrease from the baseline PASI score, has been observed in 85% of patients. Approximately 46% of patients achieved PASI50 gradually during therapy; after 4, 8 and 12 weeks of treatment 14%, 29% and 71% of patients in the 200 mg twice daily cohort achieved PASI50. PASI50 was achieved in 42% and 29% of patients taking 400 mg once daily or 400 mg twice daily, suggesting a potential clinical benefit of using a lower KD025 dosage regimen. No SAEs were reported, except for an increase in liver enzymes, which was reversible with the discontinuation of the drug (as reported in seven patients).[256]

Although ROCK2 inhibitors represent an innovative therapy, further scientific evidence regarding efficacy and safety is needed to provide a future therapeutic strategy for the management of patients with moderate to severe psoriasis.

Other IL-23 inhibitors

Mirikizumab is a monoclonal antibody selective for IL-23p19 acting on the IL-23–T_H17 pathway.[257] In the phase III OASIS-1 trial (n=530), PASI75/PASI90/PASI100 responses at week 16 were 82.5%, 64.3% and 32.4% *versus* 9.3%, 6.5% and 0.9% with placebo (p<0.001); sPGA 0/1 was achieved in 69.3% *versus* 6.5% of patients.[257,258] Responders re-randomized to different maintenance regimens maintained high responses at week 52 (PASI90 up to 86%).[258] In OASIS-2 (n=1465), PASI90 at week 16 was 74.4% with mirikizumab *versus* 6.3% with placebo but not superior to secukinumab.[259] Safety data included rare cardiovascular events such as myocardial infarction.[260] Development of mirikizumab for psoriasis was discontinued in 2021, though results confirm the efficacy of IL-23p19 blockade.[258]

IBI112, another IL-23p19 antibody, showed efficacy in preclinical models,[261] and a phase I trial in 46 patients showed no SAEs.[262] A phase III, multicentre, randomized, double-blind, placebo-controlled clinical trial with randomized discontinuation and retreatment has recently been completed to evaluate the efficacy and safety of subcutaneous injection of IBI112 in the treatment of moderate-to-severe plaque psoriasis.[263]

Icotrokinra is an oral peptide with high affinity for the IL-23 receptor.[263] The FRONTIER-1 (NCT05223868) trial, a phase IIb study evaluating the efficacy and safety of icotrokinra in patients with moderate-to-severe psoriasis, showed a significant dose–response effect at week 16 and a greater efficacy of icotrokinra than placebo.[263] FRONTIER-1 participants received icotrokinra at doses from 25 mg daily to 100 mg twice daily or placebo through week 16. Subsequently, patients completing FRONTIER-1 could enrol in FRONTIER-2 and continue icotrokinra at the same dose through week 52. Those on placebo crossed over to icotrokinra 100 mg daily for weeks 16–52. High response rates and improved patient-reported outcomes observed with icotrokinra in FRONTIER-1 were maintained throughout the year of treatment in FRONTIER-2. At week 52, 76% of patients achieved PASI75 with 100 mg twice daily.[264] The percentages of patients who achieved a PASI90 and PASI100 response at week 16 (e.g. 60% and 40%, respectively, in the group treated with 100 mg twice daily) were mostly unchanged at week 52 (e.g. 64% and 40%, respectively, in the group treated with 100 mg twice daily); SAEs occurred in 4% of patients.[264] Due to the positive results obtained in FRONTIER-1 and FRONTIER-2, two phase III clinical trials are currently under way (ICONIC-LEAD and ICONIC-TOTAL).[265,266]

IL-36R inhibitors

IL-36 is a member of the IL-1 family, which activates NF-κB and MAPK pathways through the MyD88–IRAK complex.[267] The IL-36 family of cytokines includes the three agonists (IL-36α, IL36β and IL-36γ) and one antagonist (IL-36RA).[268] Loss-of-function mutations in the *Il36ra* gene have been detected in a severe form of generalized pustular psoriasis (GPP) and plaque psoriasis.[269] Todorović

et al. demonstrated that A-552, a small-molecule inhibitor of IL-36, effectively inhibits IL-36γ and the production of other IL-36γ-induced cytokines in human and murine cells.[270] Spesolimab is a monoclonal antibody targeting the IL-36 receptor and is currently approved by both the FDA (September 2022) and EMA for the treatment of GPP flares in adults. Its approval was based on the pivotal phase II Effisayil-1 trial, in which 53 patients experiencing a moderate-to-severe GPP flare were enrolled. After 1 week of treatment, 54% of patients receiving spesolimab achieved a GPP Physician Global Assessment pustulation score of 0, compared with only 6% in the placebo group ($p<0.001$). Moreover, 43% of treated patients achieved a clear or almost clear overall GPP Physician Global Assessment score *versus* 11% with placebo ($p=0.02$).[271] A 5-year open-label extension study (Effisayil-2) is ongoing to assess the long-term efficacy and safety of spesolimab in preventing GPP flares.[272] The low incidence of GPP and limited evidence regarding treatment with spesolimab pose a challenge in determining its efficacy in a real-life setting. A review of real-world experience by Cardenas-de la Garza et al.[273] included a total of 62 patients with GPP who were treated with spesolimab. Of these, 6% of patients were aged >75 years and 8% patients were aged <18 years, with a mean age of 49.3 years (SD 20.5); 30 patients showed concomitant plaque psoriasis. Complete GPP remission was observed in 35/62 (56%) patients, 21 of whom achieved it within a week. Partial remission was defined in 27 of the 62 (44%) patients. GPP recurrence after treatment was observed in seven patients. There was a low incidence of AEs, with only eight patients reporting laboratory abnormalities, infections and erythema multiforme. Moreover, spesolimab showed the potential to provide significant and rapid symptom resolution even in patients resistant to conventional therapies. However, data on the impact of spesolimab in patients with concomitant plaque psoriasis and psoriatic arthritis are still limited, and it remains unclear whether the recurrence of plaque psoriasis can be effectively prevented with spesolimab.[273]

Currently, imsidolimab, a monoclonal antibody targeting the IL-36 receptor, is in phase III clinical trials. An open-label, single-arm, multiple-dose study was conducted in eight patients affected by GPP (of whom six completed the entire treatment cycle) who received an intravenous dose of imsidolimab 750 mg on day 1, followed by three subcutaneous doses of 100 mg administered on days 29, 57 and 85. The first responses were observed as early as day 3, with continuous improvement until day 113. Only two SAEs were reported.[274] The phase III clinical trial GEMINI-1 pointed out that 53.3% of patients receiving a single 750 mg IV dose of imsidolimab achieved clear or almost clear skin by week 4, compared to the 13.3% response rate in the placebo group ($p=0.0131$), also associated with a strong safety profile for imsidolimab.[275]

Therefore, anti-IL-36 agents hold significant potential in the treatment of psoriasis, and further research is needed to evaluate their efficacy and safety.

JAK inhibitors

JAKs represent intracellular kinases that activate STAT proteins, which translocate to the nucleus and are responsible for the synthesis of inflammatory nuclear factors. The JAK family includes JAK1, JAK2, JAK3 and TYK2, whilst STAT signalling involves STAT1, STAT2, STAT3, STAT4, STAT5 (STAT5A and STAT5B) and STAT6. In psoriasis, a key role is played by the IL-23 receptor, which relies on a heterodimer of JAK2 and TYK2 as well as on STAT3 for signal transduction.[264]

TAK-279 (zasocitinib), a highly selective oral TYK2 inhibitor, is approximately 1.3 million times more selective for TYK2 than JAK1 and is currently in a phase IIb, randomized placebo-controlled trial (NCT04999839).[276] In this study, 259 patients were randomized (1:1:1 ratio) between five zasocitinib dosage groups of 2, 5, 15 and 30 mg QD, and placebo to evaluate the efficacy and safety of zasocitinib in the treatment of moderate-to-severe plaque psoriasis. At week 12, a significantly higher percentage of patients treated with zasocitinib achieved PASI75 (44%, 68% and 67% taking 5 mg, 15 mg and 30 mg, respectively) and PASI90 (21%, 45% and 46%, respectively) compared to the placebo group (PASI75 6%; PASI90 0%). However, no statistically significant differences were observed in the 2 mg group in terms of PASI75 (18%) and PASI90 (8%) at 12 weeks compared to placebo. The majority of AEs were mild to moderate. To date, three phase III clinical trials are ongoing to evaluate the efficacy, safety and tolerability of zasocitinib in the treatment of moderate-to-severe psoriasis compared to deucravacitinib, apremilast and placebo.[277–281]

VTX958 is a selective allosteric inhibitor of Tyk2. Bank conducted a randomized, placebo-controlled, phase II study to evaluate the efficacy and safety of oral VTX958 in patients with moderate-to-severe plaque psoriasis.[282] Patients were divided into four treatment groups (50 mg BID, 300 mg QD, 225 mg BID and 300 mg BID) or placebo. At week 16, the two high doses of VTX958 (225 mg BID and 300 mg BID) achieved significantly superior PASI75 response rates than placebo, without SAEs.[280] However, the study is currently terminated.[283]

Tofacitinib is a JAK inhibitor that demonstrated superiority over placebo in the treatment of plaque psoriasis in phase III studies (OPT Pivotal 1 and 2; OPT Retreatment) but never received FDA approval due to long-term

efficacy and safety concerns.[284] However, it received approval in 2017 for the treatment of PsA resistant to methotrexate or other disease-modifying antirheumatic drugs following evidence of its efficacy in the phase III OPAL Broaden and OPAL Beyond studies.[284] Upadacitinib is a JAK inhibitor used against PsA whose efficacy has been demonstrated in the phase III studies SELECT-PsA 1 and SELECT-PsA 2. In these studies, the American College of Rheumatology's criterion for a 20% improvement in the condition of a patient with rheumatoid arthritis was achieved by a higher percentage of patients receiving upadacitinib compared to the placebo group.[285–288] Furthermore, improvements in PASI75 were also recorded. In the literature, there are case reports demonstrating the efficacy of upadacitinib in the treatment of eczematous psoriasis unresponsive to biological drugs.[283,284] However, data are currently lacking, so it remains only a potentially valid strategy in the treatment of plaque psoriasis.[285–288]

Jaktinib is a JAK1 and JAK2 inhibitor that was evaluated in a multicentre, randomized, double-blind, placebo-controlled, phase II study, which has been completed, where patients were divided into four groups, receiving two daily doses of 50, 75 or 100 mg of jaktinib or placebo for 24 weeks.[289,290] ESK-001 is a highly selective allosteric inhibitor of TYK2. It was first evaluated in phase I trial, with promising results.[291] The STRIDE phase II clinical trial on ESK-001 met its primary end point, showing significant improvements in PASI75 at week 12 for all clinically relevant doses. The maximal efficacy was observed in the highest dose arm (40 mg BID). The drug exhibited a favourable safety profile.[292] Currently, a phase II clinical trial open-label extension study is under way to evaluate the long-term efficacy and safety of ESK-001 in the treatment of plaque psoriasis.[293] Since the TYK2 inhibition pathway appears promising, several molecules are currently being studied to evaluate their effectiveness in treating psoriasis;[289] amongst these are BMS-986322 (NCT05730725 phase II study, completed)[294] and BMS-986202 (NCT02763969 phase I study, completed),[295] both of which are TYK2 inhibitors, and TLL-018 (NCT05772520 phase II study, completed), which is a highly specific inhibitor of JAK1 and TYK2.[296]

PDE4 inhibitors

PDE4 inhibitors are being investigated for use against moderate-to-severe psoriasis. Orismilast, an oral PDE4 inhibitor, has shown promising results in psoriasis treatment. In a phase IIa trial with 36 patients, 44.4% of those receiving orismilast 30 mg twice daily reached PASI75 after 16 weeks compared to 5.6% with placebo; reported side-effects included nausea (61.1% *versus* 5.6% with placebo) and diarrhoea (50% *versus* 0%).[297] A larger phase IIb study with 202 patients tested doses of 20, 30 and 40 mg twice daily, achieving PASI reductions of 52.6%, 61.2% and 63.7% *versus* 17.3% with placebo. The most frequent AEs were diarrhoea, nausea and headache, with higher doses linked to more treatment discontinuations.[298] Currently, no phase III trials have been initiated to further confirm long-term safety and effectiveness.

Mufemilast, an oral PDE4 inhibitor, has been studied for its potential in moderate-to-severe plaque psoriasis. A phase II trial with 216 patients compared doses of 15, 30 and 60 mg twice daily against placebo but the findings have not been published despite completion in 2021.[299] A subsequent phase III trial enrolled 306 participants, with 204 receiving 60 mg twice daily and 102 receiving placebo for 16 weeks, after which PASI75 response rates were to be assessed. The placebo group later switched to active treatment for an additional 36 weeks. This trial was completed in July 2023 but the efficacy and safety outcomes remain undisclosed.[300]

Roflumilast, a PDE4 inhibitor already approved for chronic obstructive pulmonary disease and in topical form for psoriasis, has also been tested orally in this disease. In the PSORRO phase II trial with 46 participants, 35% of those on roflumilast reached PASI75 after 12 weeks, whilst none in the placebo group did. After 24 weeks, PASI50, PASI75, PASI90 and PASI100 were achieved by 65%, 44%, 22% and 9% of patients, respectively. The most frequent side-effects included gastrointestinal issues, headaches, insomnia and weight loss, leading to discontinuation in 8.7% of patients.[301] No further studies are currently ongoing.

Preclinical data of ME3183, another PDE4 inhibitor, indicated that it was markedly more effective than apremilast in suppressing inflammatory cytokines. A phase II study in 132 patients with plaque psoriasis tested several regimens over 16 weeks: PASI75 was achieved in 58.3% (5 mg BID), 61.5% (7.5 mg BID) and 52.0% (15 mg OD) *versus* 14.8% with placebo, whilst the 10 mg OD group showed no clear benefit. Reported AEs mainly included nausea, diarrhoea and headaches.[302] At present, no further trials of ME3183 are ongoing in psoriasis.

Oral IL-17 inhibitors

Secukinumab, ixekizumab, brodalumab and bimekizumab are biologic drugs already approved for moderate-to-severe psoriasis and have achieved considerable results in terms of efficacy and safety. The goal of future studies for this class is to obtain molecules that can be taken orally.

DC-806 is an oral IL-17A inhibitor that has shown encouraging early results in psoriasis. In a phase I trial with 40 participants, those receiving 800 mg twice daily achieved a PASI reduction of 43.7% on average after

4 weeks, compared to 13.3% in the placebo group. Reported side-effects were all mild or moderate and showed no relation to dosage.[303] A phase IIb study involving 229 patients with moderate-to-severe plaque psoriasis was launched in May 2023 to assess multiple dosing regimens over 12 weeks but its findings have not yet been released.[304] DC-853, a next-generation oral IL-17A inhibitor derived from DC-806, entered a phase I trial in March 2024 to test single and multiple doses in 30 healthy volunteers, with results still pending.[305] Similarly, LEO 153339, another oral IL-17 inhibitor, was studied in a phase I trial with 108 healthy participants assessing safety and tolerability at different dose levels. This trial ended in July 2022 but no data have been disclosed so far.[306]

Others

Piclidenoson, an oral A3AR agonist, has undergone several clinical trials for moderate-to-severe psoriasis. In inflammatory diseases, such as psoriasis and Crohn's disease, overexpression of A3AR on the lymphocyte membrane has been observed.[307] In a phase II study with 76 patients, the 2 mg twice-daily group showed the best outcome, reaching a 35.3% PASI50 rate at week 12, with statistically significant improvements over placebo.[308] A larger phase II/III trial with 293 participants later demonstrated that, by week 32, 63.5%, 35.5%, 24.7% and 10.6% of patients achieved PASI50, PASI75, PASI90 and PASI100, respectively, with good tolerability and no major side-effects.[309] A subsequent phase III trial including 528 patients compared piclidenoson (2 and 3 mg), apremilast and placebo; whilst early results in 2022 were encouraging, quality control concerns were raised by the FDA.[310] In 2023, both FDA and EMA approved new phase III trials to further evaluate its efficacy and safety in psoriasis.

Vibozilimod (SCD-044) is an oral sphingosine-1-phosphate (S1P) receptor 1 (S1PR1) modulator being developed for psoriasis and atopic dermatitis. S1PR1 is highly expressed in lymphocytes, and binding with S1P is involved in the migration of these cells to inflamed tissues, as occurs in psoriasis.[307] In an unpublished phase I study, it showed activity by lowering lymphocyte counts in healthy volunteers.[311] A phase II trial (SOLARES-PsO-1) is currently ongoing in 240 patients with moderate-to-severe plaque psoriasis, testing three different dosing regimens against placebo. The study aims to assess both efficacy and safety but results are not yet available as completion is still pending.[312]

RGRN-305 (CUDC-305) is an oral HSP90 inhibitor. In preclinical models, it reduced inflammatory cytokines, such as TNF and IL-23, and showed promising efficacy in a xenograft mouse model.[313] A phase Ib proof-of-concept trial enrolled 11 patients treated with 250 mg or 500 mg daily: after 12 weeks, six participants achieved ≥50% PASI improvement (71–94% reduction from baseline).[314] Whilst four patients on the higher dose developed an exanthematous rash, no SAEs occurred. Transcriptome analysis further confirmed downregulation of TNF and IL-17-related inflammatory pathways.[314] Therefore, HSP90 inhibition is considered a potential therapeutic avenue for psoriasis and other immune-mediated skin diseases.

Several studies are demonstrating the relationship between alterations in the gut microbiota and systemic inflammatory diseases.[307] Therefore, certain oral antimicrobials are being investigated for the treatment of psoriasis. KBL697 is an oral probiotic derived from a live strain of *Lactobacillus gasseri* developed to modulate the gut microbiome. A phase I trial in 36 healthy volunteers tested its safety and tolerability,[307] and a phase II study in 80 patients with plaque psoriasis compared low and high doses for efficacy and safety.[307] Results from these trials have not yet been released. EDP1815 is a non-live preparation of *Prevotella histicola* that modulates the immune system in the small intestine to promote anti-inflammatory responses. Preclinical studies in murine models of T_H1-mediated and T_H17-mediated inflammation showed reductions in systemic inflammation.[307] In a phase I trial, patients with psoriasis receiving low-dose or high-dose EDP1815 had average Lesion Severity Score reductions of 23% and 15% after 4 weeks, compared to a 1% increase in placebo, with no significant AEs.[315] In a phase II trial with 249 patients, daily doses of 1, 4 or 10 capsules led to PASI50 response rates of 29.7%, 31.9% and 25.0% *versus* 12.1% in placebo; 60% of responders maintained improvement at 24 weeks. No SAEs were reported, and no further trials are currently ongoing.[316]

Discussion

This review presents a comprehensive analysis of currently approved biologics and small molecules for the management of psoriasis, providing an in-depth assessment of the existing treatment landscape whilst highlighting its limitations, such as the lack of biomarkers, which could predict treatment response and AEs. Despite the advancements in the psoriasis armamentarium, unmet needs persist, necessitating the exploration of novel and emerging therapies. In this context, new and emerging drugs have been discussed herein to offer readers a wide overview on currently available and forthcoming therapeutic innovations in the psoriasis landscape.

The advent of biologic therapies has significantly revolutionized the management of psoriasis; particularly, the latest biologic classes approved (anti-IL-17 and anti-IL-23) have demonstrated high effectiveness and

safety profiles. These treatments have set new standards in achieving long-term disease control (complete or almost complete clear skin) with minimal side-effects, making them preferable options for many patients with moderate-to-severe psoriasis.

Similarly, despite their lower effectiveness compared to certain biologics, deucravacitinib and apremilast offer a valuable option in patients preferring oral administration, especially those experiencing injection site reactions or with needle phobia. Notably, real-life data on deucravacitinib are still emerging due to its recent approval. Moreover, the future introduction of RORγt and ROCK2 inhibitors, as well as oral anti-IL-23 agents, may provide new oral therapeutic options.

Despite the wide range of available therapies, unmet needs still exist, particularly in patients with moderate-to-severe plaque psoriasis and in specific clinical phenotypes such as pustular psoriasis, where a different pathogenesis has been identified, highlighting the need for drugs targeting the IL-36 axis, such as spesolimab, alongside other investigational therapies.

Globally, new drugs are desirable to offer patients a more personalized approach. This patient-centred approach is in line with the current trend in dermatology towards individualized therapy, where the goal is not only to achieve skin clearance but also to improve overall QoL.

Paradoxical reactions may occur during psoriasis treatment with biologics. Amongst these, eczematous paradoxical reactions are more frequently observed with anti-IL-17, often requiring treatment switching. JAK inhibitors appear to be a valuable option in individuals developing eczematous reactions or patients affected by both psoriasis and atopic dermatitis. A key immunological consideration is the shift between T_H1 and T_H2 pathways during cytokine-targeting treatments. Blocking specific cytokine axes can lead to imbalances and rebound loops, which may contribute to paradoxical reactions or secondary inefficacy. This phenomenon underscores the urgent need for predictive biomarkers to optimize treatment selection and minimize AEs. In the future, advances in pharmacogenetics and artificial intelligence could revolutionize psoriasis management. Artificial intelligence-driven models integrating clinical data, laboratory findings and biomarkers could provide a more objective approach to therapy selection. This would enhance precision medicine by guiding treatment choices and helping establish standardized therapeutic algorithms for first-line, second-line and third-line options.

As regards topical therapies, the introduction of novel topical agents may overcome the limitations associated with the use of topical corticosteroids, particularly for sensitive areas such as the genital region, face or skin folds, where their use is contraindicated. Additionally, new topical drugs could offer more effective and safer solutions as compared with currently available treatments.[273]

It should be considered that there are still patients with psoriasis unresponsive to currently available biologics and small molecules, or with contraindications to these drugs, where the treatment opportunity landscape is limited. Unfortunately, there are no biomarkers that can predict therapeutic outcomes, leading to the considerations of several factors before starting treatment. In this context, a diverse therapeutic armamentarium is essential to ensuring that patients receive the right treatment at the right moment. These biomarkers would be also desirable for the collection of evidence-based data to guide the dermatologist in treatment switching (intra-class or inter-class switching) as well as to support treatment selection for the prevention of transition from psoriasis to psoriatic arthritis and of cardio-metabolic comorbidities. Psoriasis management may be challenging, particularly in complex cases. Therefore, the availability of new drugs, both systemic and topical, will be crucial in overcoming current limitations, and providing patients with the most personalized and precise therapeutic approach possible.

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