Investigational systemic drugs for moderate to severe plaque psoriasis: What's new?

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Abstract

Introduction: The therapeutic armamentarium for the treatment of psoriasis, a chronic inflammatory skin disease, is now reasonably broad and structured, with several therapeutic agents that demonstrated a successful long-term control of this condition. However, there are still unfulfilled gaps resulting from the inherent limitations of existing therapies, which have paved the way for the identification of new therapeutic strategies or the improvement of the existing ones.

Areas covered: The aim of this review is to thoroughly explore new therapeutic strategies and novel drugs that are currently in the pipeline for the treatment of psoriasis, focusing primarily on agents that are currently in phase I/II of clinical development. Some of which retrace already existing therapeutic approaches, such as the IL-23/Th17 pathway inhibition, while others unveil new and yet unexplored ones.

Expert opinion: Since the therapeutic landscape of psoriasis is wide, it is not yet clear whether novel agents will fill the remaining gaps in the context of a broader and more diversified set of oral and biologic therapies. Nevertheless, with the development of precision medicine approaches, the development of innovative targeted drugs will still have a therapeutic rationale in psoriasis.

Key words: biologics, JAK inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, monoclonal antibodies, clinical trial, plaque psoriasis, small molecules, systemic treatments.

Article highlights:

- Psoriasis is a highly prevalent chronic inflammatory skin disease. In recent years, deeper understanding the molecular and cellular pathways involved in pathophysiology have led to the emergence of highly effective targeted therapeutic drugs with potential for enhanced disease control.
- Novel drugs, currently under investigation in phase I and II trials, explore existing therapeutic targets, such as the IL-23/Th17 pathway inhibition, phosphodiesterase-4, and JAK inhibitors, along with new unexplored ones, including retinoic acid receptor-related orphan receptor γt (RORγt) and Heat Shock Protein (HSP)90 inhibitors.
- Whether the preliminary results achieved by these new agents will be confirmed in phase III studies, future treatment scenarios may rely on a diversified armamentarium with a more diversified set of oral and biologic therapies to help the physician personalize the therapeutic approach.

1. Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disease characterized by a multifactorial etiology and a broad spectrum of clinical manifestations. The disease is equally frequent in both sexes and the worldwide prevalence ranges from 0.51% to 11.43% in adults, and from 0% to 1.37% in children [1].

The most common clinical presentation of psoriasis consists of symmetrically distributed erythematous plaques with sharply defined margins (plaque psoriasis), other subtypes, including erythrodermic, pustular, guttate, inverse, and palmoplantar psoriasis exist, though less frequently observed. Peculiar body districts may also be affected, ranging from nails, scalp, to mucosal areas[2]. Moreover, around 30% of patients with psoriasis may exhibit concomitant arthritis, namely psoriatic arthritis, which can present as oligoarthritis, enthesitis, spondylitis, or dactylitis[3].

No longer considered an immune disease confined to the skin, psoriasis is now deemed a systemic inflammatory disorder associated with variable comorbidities such as cardiovascular disorders, diabetes, metabolic syndrome, and depression[4].

Moreover, psoriasis lesions may be localized in visible areas, having negative psychological consequences and a significant impact on patients' quality of life. Patients may experience social stigmatization and isolation and may face difficulties in finding a new employment[5]. The psychological burden of psoriasis is even higher if arthritis is concomitant.

2. Current pathogenic model in psoriasis

The pathogenesis of psoriasis has been a flourishing field of scientific research. Initially thought to be a primary keratinization disorder, the dysregulation of the immune system is now recognized as the central core of psoriasis pathogenesis, which indeed relies on a complex interplay between genetic and immunological factor[6].

In detail, the major alterations involve the genes encoding HLA (human leucocyte antigen) class I antigen *HLA-Cw6*, particularly the *HLA-C*06:02* variant[7], which plays a role in CD8+ T cells functioning[8]. Polymorphisms in the ERAP gene, encoding an enzyme involved in HLA class I antigen presentation, have been shown to increase the risk of developing psoriasis[9]. Moreover, some variants of both interleukin(IL)-23 and IL-23R genes have been reported to predispose to psoriasis, while an IL-23R variant seems to protect against the disease[10].

Both innate and adaptive immunity contribute to the inflammation in psoriasis in a complex feed-forward circuit that is intended to amplify the inflammatory process resulting in the main histopahtological changes seen in psoriasis, such as keratinocyte proliferation with parakeratosis, angiogenesis, neutrophil infiltration and Th1/Th17 cells enrichment[11].

Several autoantigens have been implicated in the initiation of the immune-mediated response, particularly the melanocyte antigen ADAMTSL5[12], the cathelicidin antimicrobial peptide LL37[13], and KRT17[14].

First to be activated are the cells of innate immunity such as macrophages and dendritic cells, which in turn produce several mediators including TNF-α, IL-12, IL-23, and type I interferon (IFN). While IL-12 and IL-23 are mainly produced by myeloid (mDC)[15], driving the differentiation of Th1 and Th17 subpopulations, respectively, while type I IFNs are secreted by plasmacytoid dendritic (PDC)[10][10]. The activation of pDC starts the inflammatory process in psoriasis through the production of type I IFN (IFN-α and IFN-β). Type I IFN signaling (i.e., IFN-α) promotes mDC maturation, acting as upstream cytokine in the IL-23/IL-17 axis[16].

IL-23 belongs to the IL-12 family, consisting of several members characterized by heterodimeric structure. Both IL-12 and IL-23 share a common subunit (IL-12p40) and are produced by antigen presenting cells, mostly macrophages and myeloid dendritic cells. Whilst IL-12 is a key element in the induction of IFN-γ production and Th1 differentiation, IL-23 has been shown to drive the maturation and expansion of Th17 cells[17]. IL-12 and IL-23 bind to their cognate receptor complexes, formed by a shared chain (IL-12Rβ1) and a second chain named IL-12Rβ2 and IL23R, respectively. Upon binding to their receptors, both cytokines activate the same Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling molecules (JAK2, TYK2, STAT1, STAT3, STAT4 and STAT5)[18]. Interestingly, STAT3 induces the expression of RORγ, a transcription factor which is in turn involved in enhancing IL-17A, IL-17F, IL-22, and IL-23R gene expression[19,20].

Most of these cytokines, namely IL-17A and IL-17F, are responsible for skin inflammation, together with other proinflammatory molecules such as TNFα that shows synergistic effects with IL-17A inducing the expression of several other inflammatory mediators[21]. TNFα signals by binding to two different receptors, named TNFR1 and TNFR2, and activates the intracellular NF-κB signaling pathway[22,23].

Once triggered, the inflammatory process is maintained by a few closely intertwined molecular pathways generating a positive feedback loop. In detail, three major circuits seem to contribute the most to psoriasis pathogenesis: the IL23/Th17, the IFN, and the IL-1/IL-36 axis.

The production of IL-23 by myeloid dendritic cells induces the expression of IL-17A as well as IL-17F that homo- or heterodimerize to form functional IL-17F or IL-17A/F[24]. Both these molecules bind to the same receptor composed of IL-17RA and IL-17RC subunits and activate the NF-κB pathway. These cytokines mostly exert their effects on keratinocytes, inducing their proliferation and production of IL-17C and IL-36[25].

The role of IL-36 in psoriasis has received great attention when loss-of-function mutations in the gene IL36RN, encoding the anti-inflammatory molecule IL-36Ra, were described in pustular variants of psoriasis[26]. IL-36 cytokines, belonging to the IL-1 superfamily, are expressed predominantly by epithelial cells, particularly keratinocytes, and act on several target cells, including keratinocytes themselves and neutrophils, stimulating their recruitment in the skin and, thus, contributing to the so-called feed-forward inflammatory circuit in psoriasis[27].

Furthermore, IFN-γ is mostly produced by Th1 cells and establishes a positive feedback loop by enhancing the expression of CXCL9 and CXCL10 chemo-attractants, which are responsible for the further enrollment of Th1 cells to the site of inflammation, as well as by directly targeting keratinocytes[28]. These cells finally respond to these stimuli by proliferating and amplifying inflammation through the production of other cytokines [i.e., IL-36γ, TNFα, IL-17C, IL-19, (thymic stromal TSLP), chemokines (i.e., CCL20, CXCL1, CXCL8-11), growth factors (EGF, VEGF, and HBEGF), and other pro-inflammatory products, such as antimicrobial peptides[29].

Most of the soluble mediators involved in the pathogenesis of psoriasis, such as IL-12, IL-23, IL-22, IFN-α, IFN-β, IFN-γ, exert their effects upon binding to a specific receptor which initiates intracellular signaling through the JAK/STAT pathway[30]. The JAK family consists of four cytoplasmic tyrosine kinases: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), while STAT members (STATs) include seven isoforms: STAT1, STAT2, STAT3, STAT4, STAT5A/B, and STAT6[31]. For example, IL-23 acts through the Tyk2-JAK2 pathway and STAT3 recruitment and activation, which leads to transcription of other inflammatory mediators[32]. The discovery of the central role of the JAK/STAT pathway in cytokine-mediated inflammation in psoriasis has posed the basis for investigations of JAK proteins as potential therapeutic targets for the treatment of the disease[33].

Given the pathogenetic complexity of the disease, numerous therapeutic strategies have been proposed and approved so far or are currently being investigated for the treatment of psoriasis .

3. Current therapeutic strategies

Psoriasis can manifest with different degrees of severity, usually estimated in daily clinical practice using dedicated scores, such as the PASI (Psoriasis Area and Severity Index) score[34], or body surface area (BSA). The choice of the right treatment option varies according to multiple factors such as disease severity, comorbid conditions, previous antipsoriatic therapies and psoriatic arthritis, in order to tailor the treatment for each patient.

Mild forms, typically involving less than 3-5% of the BSA, can generally be managed with topical therapies based on steroids, vitamin D analogues, calcineurin inhibitors, keratolytics, and phototherapy[35]. Conversely, systemic treatments are the mainstay of treatment of moderate (5-10% BSA) and severe (>10% BSA) psoriasis as well as in the case of involvement of the so-called "sensitive and visible" areas, such as the face, palms and/or soles, and genital areas.

Systemic agents encompass traditional immunosuppressive agents, such as cyclosporine and methotrexate, retinoids, fumaric acid esters and orally administered small molecules, such as apremilast.

In recent years, increasing insights on psoriasis's pathophysiology has led to the identification of new potential therapeutic targets and thus the development of highly selective and effective biotechnological agents, administered subcutaneously or intravenously, which have completely transformed the therapeutic landscape of moderate-to-severe psoriasis[36].

Currently approved biological agents indeed antagonize at different levels some of the key cytokine pathways involved in psoriasis pathogenesis, namely, TNFα, IL-12/23, and IL-17.

TNFα inhibitors are the first class of drugs to be investigated and marketed for the treatment of psoriasis. Among these, infliximab[37], adalimumab[38] and certolizumab[39] are monoclonal antibodies, while etanercept[40] is a soluble receptor built as a fusion protein of the extracellular portion of TNFR-2 linked to a Fc portion of a monoclonal antibody[41].

IL-17 inhibitors encompass four monoclonal antibodies: secukinumab[42] and ixekizumab[43], which selectively targets IL-17A; brodalumab[44], which targets the IL-17RA subunit thus blocking the signaling of IL-17A, IL-17C, IL-17E and IL-17F; and bimekizumab, an anti-IL-17A, IL-17F, and IL-17A/F monoclonal antibody, which has so far received only EMA[45] and not FDA approval.

Finally, antagonism of the IL-12/23 is currently performed by four mAbs: ustekizumab[46], guselkumab[47], tildrakizumab[48] and risankizumab[49]. Ustekinumab is able to inhibit the shared p40 subunit of interleukin (IL)-12 and IL-23, while the others mAbs selectively target the p19 subunit, specific to IL-23.

Beside biologic agents, there is one small molecule approved for the treatment of psoriasis represented by apremilast. Apremilast is an orally administered phosphodiesterase 4 (PDEA4)

inhibitor and is the only one in its class to be approved for the treatment of moderate-to-severe psoriasis[50]. PDEA4 is an enzyme expressed in keratinocytes and immune cells which hydrolyzes cyclic adenosine monophosphate (cAMP), a second messanger involved in immunomodulatory pathways[51].
Although several treatment options for plaque psoriasis are currently available, response rates may vary considerably and there is still a proportion of patients resistant, intolerant, or contraindicated to multiple therapies, representing a persistent unmet need in the therapeutic paradigm.

This review aimed to explore new therapeutic strategies and novel drugs that are currently in the pipeline for the treatment of psoriasis, focusing primarily on agents that are currently in earlier phases of clinical development (phases I and II), dissecting their mechanism of action, safety, and efficacy data. Data were collected conducting a search in the published literature through December 20, 2022, that included original articles using the PubMed database, and clinical trial data published on ClinicalTrials.gov. The terms used for the PubMed search were as follows: "Psoriasis" AND "systemic treatment", OR "target therapy", OR "biologics", OR "JAK inhibitors", OR "pipeline", OR "Aryl hydrocarbon Receptor modulator", OR "Phosphodiesterase 4 inhibitors", OR "Receptor antagonists", OR "Fumaric acid esters", OR "Heat Shock Protein 90 Inhibition", OR "ROCK2 Inhibition".
The authors selected articles that outlined novel insights into psoriasis and systemic treatments in the pipeline.

3.1. Biologics

Several biological agents are being investigated for the treatment of psoriasis in either phase I or II trials (Table 1). Some of them own molecular structure, therapeutic target, mode-of-action, route of administration similar to already existing agents, while others unveil new and unexplored therapeutic strategies (Figure 1).
In detail, three drugs antagonizing the IL-17 pathway are currently being tested. ABY-035/AF02 (Izokibep) is a small molecule drug that acts as a selective, potent, inhibitor of IL-17A, to which it binds with high affinity. The drug has already completed a phase II clinical trial in patients with psoriatic arthritis with promising results[52] and is currently being investigated in a phase II clinical trial with the indication of plaque psoriasis (NCT03591887).

Sonelokimab (M1095/ALX-0761) is a nanobody targeting both IL-17A and IL-17F. Nanobodies represent a novel class of therapeutic agents composed of single-domain antibody fragments derived from the variable domain of heavy chain-only antibodies. In comparison with large-sized canonical antibodies, composed by four-molecular chains and therefore unstable, nanobodies can combine the advantages of small proteins with the benefits of monoclonal antibody properties[53]. In detail, sonelokimab is a trivalent nanobody composed of three monovalent moieties. The N-terminal moiety binds to IL-17F, the C-terminal moiety binds to IL-17A and IL-17F, and a central moiety binds to serum albumin. The drug has been recently investigated in a phase IIb trial, in which participants were randomly assigned to receive placebo, sonelokimab 30 mg, sonelokimab 60 mg, sonelokimab 120 mg normal load, sonelokimab 120 mg augmented load, or secukinumab 300 mg. The primary outcome was the proportion of participants in the sonelokimab group achieving an investigator global assessment (IGA) of clear or almost clear (score 0 or 1) at 12 weeks compared with the placebo group. At week 12, none of the participants in the placebo group achieved the primary outcome, in comparison with 48,1% in the sonelokimab 30 mg group, 84,6% in the sonelokimab 60 mg group, 77,4% in the sonelokimab 120 mg normal load group, 88,2% in the sonelokimab 120 mg augmented load group and 77,4% in the secukinumab group[54]. Patients receiving higher dosage of the drug (60 mg and 120 mg) outperformed the sonelokimab 30 mg treatment arm. An overall percentage of 49,5% of patients experienced adverse events, slightly more frequent in the sonelokimab arms. Notably, in the time frame between week 12-52, 6,4% of patients in all sonelokimab groups experienced Candida infection, compared with 2% in the secukinumab group.

Vunakizumab (SHR-1314), a monoclonal antibody that selectively targets the subunit IL-17A, has proven to be both effective and tolerable in phase I trials. In a 36-week placebo-controlled dose-finding phase II study (NCT03463187), patients were randomized to receive vunakizumab (40, 80, 160 or 240 mg) or placebo subcutaneously, every 4 weeks, until week 12. The primary outcome was evaluated as the percentage of subjects achieving PASI75 at week 12. At this time point, an improvement of at least 75% in the PASI score was reported in all active arms compared with placebo (40, 80, 160, and 240 mg: 56.8%, 65.8%, 81.6% and 86.5%, respectively, vs 5.4%; $p<0.001$). Overall, the drug was well tolerated, and no serious adverse events were reported[55]. Following the promising results attained in the phase II program, recruitment for phase III trials is currently ongoing.

GSK2831781 is a humanized mAb, targeting the lymphocyte activation gene-3 (LAG3) protein. LAG-3 is an inhibitory transmembrane receptor (IR) that negatively regulates T-cell activation [56,57]. LAG-3 blockade is being investigated as checkpoint blockade immunotherapy for cancer

treatment[58]. However, since LAG-3 is rapidly upregulated following T-cell activation[59], the depletion of activated LAG-3+ T cells was explored preclinically as therapeutic strategy and showed to reduce skin inflammation[60]. Upon these results, GSK2831781 was tested in a phase I/Ib, double-blind, placebo-controlled clinical study on psoriatic patients and healthy volunteers, randomized to single doses of the drug (up to 0.15 and 5 mg/kg, respectively) or placebo. In this study, psoriasis disease activity improved up to day 43 at all GSK2831781 doses compared with placebo, with no safety concerns. Additionally, the expression of proinflammatory genes was found to be reduced, while the expression of genes associated with skin barrier function was increased[61].

Within immune checkpoint modulation, a novel programmed cell death (PD)-1 agonist antibody, CC-90006, has been developed and investigated in psoriasis. Like LAG-3, PD-1 is an IR involved in several mechanisms of immunological homeostasis and self-tolerance to prevent autoimmunity, including central and peripheral tolerance. The inhibition of T cell function provides the rationale in using a PD-1 agonist antibody to treat autoimmune and chronic inflammatory diseases[62]. CC-90006 safety and tolerability were investigated in a phase I trial (NCT03337022), following administration of multiple subcutaneous doses in 34 patients with mild-to-moderate plaque psoriasis but no results are currently available for this trial.

Namilumab is a novel monoclonal antibody that acts via granulocyte-macrophage colony stimulating factor (GM-CSF) neutralization. GM-CSF is a key cytokine that serves as a growth factor for granulocytes and monocytes and guides the activation, maturation, survival, and trafficking of monocyte-derived macrophages and their polarization towards a proinflammatory phenotype. Inhibition of this axis has already proven its efficacy in the management of rheumatoid arthritis and could analogously demonstrate relevance in psoriasis, considering the high expression of GM-CSF in psoriatic skin lesions and patients' serum. Namilumab could lead to a reduction in immune cell migration into the skin, thus limiting the production of proinflammatory cytokines (such as IL-23, IL-12, and IL-17), along with the inhibition of keratinocyte proliferation[63].

The drug was investigated in a phase II trial to establish namilumab efficacy and tolerability in moderate to severe plaque psoriasis, measured as PASI75 response rate at week 12, followed by a 52-week open-label extension period. 122 eligible participants were enrolled and randomly assigned to receive four dose levels of the study medication or placebo (NCT02129777).

At week 12, no significant difference emerged in the achievement of PASI75 in comparison between the four namilumab cohorts and placebo; the mean change in PASI score throughout the study was similar in all arms. Biopsy sampling was performed on lesional and nonlesional tissue

from 21 participants of all arms, including the placebo group, at baseline, week 2, and 12. No significant treatment-related differences emerged at week 12 in cell subtypes and cytokine expression within skin biopsy samples.

As concerns the safety profile, the incidence of treatment emergent adverse events (TEAEs) was comparable between namilumab and placebo cohorts and most of the TEAEs were mild. Close monitoring for pulmonary alveolar proteinosis (PAP) was performed throughout the study; no patients showed signs of PAP nor significant changes in lung function during the study. Study findings obtained from this trial do not support the therapeutic relevance of GM-CSF pathway in psoriasis and the clinical development of namilumab presumably will be withdrawn.

4.2 JAK inhibitors

JAK inhibitors (JAKi) have widely established their efficacy in the management of various inflammatory diseases, including psoriasis. Tyrosine kinase 2 (TYK2) belongs to the JAK family and mediates the intracellular signaling of IL-12, IL-23, and IFN alpha[64].

PF-06826647, a novel oral JAKi, targets with high affinity TYK2 by binding to the catalytically active Janus homolog 1 domain. The drug slightly interferes with JAK1-3-mediated signaling, involving IL-6, IL-2, and IFN gamma. A phase 2b, a randomized, double-blind, 16-week placebo-controlled, parallel-group study was designed to evaluate the efficacy, safety, and tolerability of PF-06826647 in subjects with moderate-to-severe plaque psoriasis, followed by a 24-week open-label extension period. Participants were randomized to receive a once-daily oral dose of 50 mg, 100 mg, 200 mg, or 400 mg, or placebo[65].

The main endpoint was the proportion of participants attaining > 90% PASI improvement from baseline (PASI 90) at week 16. At this time point, a significantly greater proportion of participants achieved PASI90 in the 200-mg and 400-mg groups (33%; p =0.0004 and 46.5%; p= 0.0001, respectively) versus placebo. Notably, this achievement was evident as early as week 4. The investigational drug led to a significant improvement in Peak Pruritus numerical rating scale from baseline. Consistent with previously reported data, nasopharyngitis and upper respiratory tract infection emerged as the most common TEAEs; no serious infections occurred in the study period. Herpes zoster infection, conceivable during JAKi treatment, did not emerge during the trial, suggesting that the virus activation probably involves TYK2-independent JAK signaling. No thromboembolic or major cardiovascular events occurred.

Globally, 200-mg and 400-mg PF-06826647 were superior to placebo in achieving primary and secondary outcomes with an acceptable safety profile.

4.3 Receptor antagonists

Retinoic acid-related orphan nuclear receptors, which include RORα, -β and -γ, are ligand-dependent transcription factors. The RORγT isoform represents a potential therapeutic target in psoriasis because of its role in IL-17 producing T cell proliferation and differentiation[66]. Indeed, upon IL-23-induced STAT3 activation, it stimulates Th17-mediated immune response by promoting the expression of IL-17A, IL-17F, and IL-22, and leads to a switch of naïve T cells to a T regulatory phenotype, resulting in the expression of anti-inflammatory cytokines, such as IL-10[19]. To date, several oral RORγT antagonists are under investigation. The main concern is related to safety warnings, including the occurrence of thymic lymphomas as observed with the investigational drug BMS-986251 in a preclinical study[67], and elevation of liver enzymes in humans with VTP-43742[68]. The research was therefore oriented towards finding alternative chemical structures not interfering with thymocyte maturation and without hepatic toxicity.

Some orally administered RORγT inhibitors are currently being investigated for the treatment of psoriasis, encompassing JTE-451, BI-730357, and ABBV-157.

JTE-451 is an orally administered RORγt, whose efficacy and safety were investigated throughout a 16-week placebo-controlled, parallel-group, dose-finding phase II trial (NCT03832738). One hundred fifty-two patients were enrolled and randomly assigned to receive 200-mg or 400-mg twice daily oral JTE-451, or placebo.

At week 16, a significant proportion of patients in the 400-mg cohort achieved PASI75 compared with placebo (22% and 7.8%, respectively, $p<0.035$). Adverse events were predominantly mild in nature and mainly represented by gastrointestinal manifestations; 4 cases of severe adverse events were reported, with no significant differences between the cohorts.

Along this line, BI-730357 completed a parallel group, dose-finding, phase II trial to evaluate its efficacy, tolerability, and safety in the treatment of moderate-to-severe plaque psoriasis (NCT03635099). Co-primary endpoints comprised the proportion of patients attaining PASI75 and sPGA (Static Physician's Global Assessment) 0/1 at week 12. BI-730357 was investigated at different dosing regimens, proving to have promising efficacy and favorable safety profile.

Finally, cedirogant (ABBV-157) is an oral inhibitor of RORγT, being developed for the treatment of immune-mediated diseases, among which plaque psoriasis. The investigational drug completed the dose-ranging, parallel-group phase IIb trial but results are not yet available (NCT05044234).

Additional mechanisms of action were explored including the selective inhibition of histamine receptors. Histamine (HA) is an endogenous short-acting amine that exerts its physiological functions by binding to four subtypes of G-protein-coupled receptors (GPCRs), namely H1, H2,

H3 and H4, expressed on various cell types, predominantly on the immune system cells, including eosinophils, mast cells (MCs), monocytes, dendritic cells (DCs), and T cells[69]. It exerts a pivotal role in immunomodulation and immune cell chemotaxis, both in the histamine-mediated acute inflammatory response, but also in the maintenance of chronic inflammation[70].

Hence, interest in the HA pathway as an attractive therapeutic target in chronic inflammatory diseases has risen. Han et al investigated the role of H4R on CD4+ T cells in psoriasis, proving that the receptor is highly expressed on Th17 cells. HA stimulation via H4R influences Th17 cell differentiation and key proinflammatory cytokine secretion[71].

Adriforant (ZPL-3893787) is a selective histamine H4 receptor antagonist currently investigated for the treatment of plaque psoriasis. A phase II double-blind, placebo-controlled study investigated its efficacy in moderate to severe psoriasis patients, randomized to receive either oral 30 mg ZPL-3893787 once daily or placebo once daily for 12 weeks. The primary endpoint includes the percentage change from baseline in PASI score while the secondary outcomes evaluated improvement in the IGA score throughout the study period. ZPL-3893787-treated participants did not achieve a significant mean change in PASI score compared with placebo (-28.04 vs -37.3). Similarly, no significant differences resulted in the number of PASI50 and PASI75 responders at week 12 (NCT02618616).

Additional mechanisms of action such as the antagonism of interleukin-binding receptors are under development. Among these, the IL-2 receptor antagonism is worthy of mention. IL-2, first discovered as an autocrine growth factor for cultured T-cell[72], is known to play a dominant role in T cell development [73]. CC-92252 is an IL-2 Fc fusion protein which exerts agonistic effects on IL-2R expressed on Treg cells, promoting an anti-inflammatory response. The drug has been investigated in phase I clinical trial on healthy subjects and patients with psoriasis; however, the study was terminated because progression criteria were not met (NCT03971825).

4.4 Phosphodiesterase 4 (PDE4) inhibitors

Phosphodiesterases (PDE) are intracellular non-receptor enzymes responsible for the degradation of cyclic nucleotides, such as cGMP and cAMP, which are secondary messengers crucial for the signal transduction[74]. The PDE family encompasses 11 members, including cAMP specific PDE4 that is preferentially expressed in immune epithelial cells, such as keratinocytes[75]. The blockade of PDE4 increases the intracellular levels of cAMP, downregulating the inflammatory responses[76], as observed with apremilast that has been shown to reduce plasma levels of proinflammatory cytokines including IL-17A, IL-17F, IL-22 and TNFα [77,78].

To date, apremilast is the only PDE4 inhibitory agent to be approved for psoriasis[50], but other agents with the same mode of action are currently being investigated in clinical trials.
In detail, orismilast is a new-generation PDE4 inhibitor with high selectivity for the PD4 subtypes linked to inflammation. A phase II clinical trial is currently investigating the efficacy and safety of the drug with 202 participants, randomly assigned in a 1:1:1:1 ratio to receive one of the three orismilast doses (20 mg, 30 mg, or 40 mg) or placebo BID (NCT05190419) but the results of this trial are not yet available.
Similarly, roflumilast is a selective, long-acting PDE4 inhibitor which has already proven significant efficacy in its topical administration in a phase IIb trial designed for the treatment of moderate-to-severe psoriasis[79]. Based on the promising results of topically administered roflumilast, an oral formulation at the dosage of 500 μg daily is now being tested in double-blinded, randomized, placebo-controlled phase II clinical trial on 40 patients with plaque psoriasis (NCT04549870).

4.5 Fumaric acid esters (FAE)

Systemic therapy with FAEs has been licensed in Germany since 1994 for the treatment of moderate to severe psoriasis. The mechanism of action of this class of agents is not fully understood. However, it has been shown that FAEs are able to bind to the transcription factor NrF2[80] and promote its migration to the nucleus where this molecule suppresses the transcription of pro-inflammatory genes[81]. Moreover, FAEs have been demonstrated to inhibit NF-κB translocation into the nucleus and DNA-binding, inhibiting NF-κB-dependent pro-inflammatory pathways[82].
Among FAEs, dimethyl fumarate (DMF) has received EMA approval for the treatment of plaque psoriasis in 2017[83]. Tepilamide fumarate (PPC-06), a prodrug of monomethyl fumarate (MMF), has been studied in a randomized, placebo-controlled phase IIb clinical trial[84]. A total of 426 patients were randomized to receive tepilamide fumarate 400 mg once daily or BID, 600 mg BID, or placebo. Co-primary endpoints included the proportion of patients achieving PASI75 and IGA score of 0/1 at week 24. At this time point, all treatment groups showed higher PASI75 response and IGA treatment success rate compared with placebo. In detail, PASI75 was obtained in 39,7%, 47,2%, 44,3% in tepilamide fumarate 400 mg once daily, 400 mg BID and 600 mg BID groups, with a statistically significant difference ($p<0.05$) in all treatment arms compared with placebo (20%)[84]. Half of patients in the 400 mg once daily group, 52% in the 400 mg BID, and 62% in the 600 mg patients experienced TEAEs, compared with 48% of participants in the

placebo group. The rate of TEAEs was lower compared with that observed in DMF trials (69-84%)[85,86].

Particularly, the rate of gastrointestinal adverse events was 20-42% across all treatment groups, compared with DMF trials (56-63%)[86].

4.6 New emerging therapeutic strategies

ROCK2 Inhibition

A novel therapeutic strategy for the treatment of psoriasis, related to the blockade of the IL-23/T17 pathway, is the inhibition of Rho-associated coiled-coil–containing protein kinase 2 (ROCK2). ROCKs are serine/threonine kinases that include 2 isoforms, ROCK1 and ROCK2, encoded by 2 different genes. These molecules are activated by Rho GTPases and mediate the phosphorylation of downstream targets in cells[87]. Recently, ROCK2 has been shown to be directly involved in Th17-skewing conditions and to regulate IL-17 secretion via a STAT3/IRF4/RORγt dependent mechanism in animal models and in vitro culture of human T-cells[88,89]. Moreover, in a phase I study, an oral ROCK2 inhibitor, KD025 (belumosudil), was administered in healthy human subjects and demonstrated to potently downregulate the ability of T cells to secrete IL-21 and IL-17, via a mechanism that involves regulation through STAT3, IRF4, and RORγt[90]. In this trial, the drug also showed a tolerable safety profile. Based on these promising results, a phase 2, open-label, dose-finding study was conducted to evaluate the safety, tolerability, and activity of KD025 in patients with psoriasis[91]. The drug was administered at the dosage of 200 mg BID, 400 mg once a day, and 400 mg BID for 12 weeks. Clinical amelioration, measured as any decrease in PASI score from baseline, was reported in 85% patients at week 12, and 46% of patients achieved the outcome of PASI50. Furthermore, serum levels of IL-17 and IL-23 were found to be decreased in a time-dependent manner in clinically responder patients, with a correlation between changes in PASI score and IL-17 peripheral blood levels. Results from immunostaining of skin specimens, obtained from patients throughout the trial, have demonstrated a reduced intensity of RORγt and ROCK2 staining after 12 weeks of treatment with almost no effect on the expression of ROCK[87].

KD025 at different dosing regimens was also investigated in a randomized, double-blind, placebo-controlled trial on patients with moderate-to-severe psoriasis (NCT02852967). Although the primary endpoint was not met, an improvement in clinical manifestations, measured as PASI

75 at week 16, was detected in a higher proportion of patients in KD025 group compared with the placebo group.
Further randomized trials of KD025 are needed to validate the therapeutic potential of targeted ROCK2 inhibition in psoriasis.

Heat Shock Protein 90 Inhibition

HSP90 is an ATP-dependent molecular chaperone, primarily expressed in keratinocytes and dermal fibroblasts[92]. This molecule participates in a myriad of cellular processes, such as signal transduction, intracellular transport, and protein degradation[93]. Recently, HSP90 has been demonstrated to play a role as a downstream regulator of IL-17A signaling[94], as well as to take part in the JAK/STAT signaling pathway[95].
HSP90α, the inducible isoform of HSP90, was indeed found to be significantly upregulated in epidermal keratinocytes and mast cells of lesional skin from psoriatic patients, compared with non-lesional skin and healthy controls[96]. Furthermore, other effects of HSP90 have been hypothesized to interfere with psoriasis pathogenic mechanisms, inhibiting *in vitro* human monocytic cell line, and reducing pyroptosis, a specific mode of NLRP3 inflammasome-mediated cell death[97]. Since some evidence on a contribution of the NLRP3 inflammasome in psoriasis have been reported[98], beneficial effects of HSP90 inhibition in psoriasis could be associated with the suppression of NLRP3 inflammasome-induced cell damage.
Recently, RGRN-305, a HSP90 inhibitor, has been developed and tested in vitro in human keratinocytes, demonstrating a significant suppression of several IL-17A- and TNF-induced proinflammatory genes[99]. Furthermore, the drug was orally administered in a murine model of psoriasis and showed clinical amelioration, reduced epidermal thickness, as well as decrease in levels of TNF-α and IL-17[100].
Based on these encouraging findings, the drug was further investigated in a phase I, proof-of-concept study on psoriatic patients, who were treated with RGRN-305, 250 mg or 500 mg daily for 12 weeks[101]. In this study, 6 out of 11 patients achieved the endpoint of PASI 50 at week 12, without a clear dose effect. About the safety profile, only mild AEs were reported in the 250 mg group, whereas four patients in the 500 mg group developed a mild-to-moderate exanthematous eruption. Moreover, a transcriptomic analysis on skin specimens was performed in the study, revealing a sustained reduction of TNF-α and IL-17-induced inflammatory genes, such as IL36γ and IL8, as well as a downregulation of IL23/STAT3-driven activities[99].

Oral microbials

As in other inflammatory dermatoses, the administration of oral microbials is being pursued as a promising therapeutic strategy in psoriasis, due to their potent anti-inflammatory effects.
EDP1815, for instance, is a non-live pharmaceutical preparation of a strain of *Prevotella histicola*, which has been investigated in a recently completed phase II randomized clinical trial for the indication of plaque psoriasis (NCT04603027). The trial consisted of two parts: a part A, where patients received either EDP1815 or placebo for 16 weeks, and part B, where patients were followed for up to 24 weeks after they had stopped receiving EDP1815 or placebo. The drug proved a statistically significant superior efficacy compared with placebo, measured as the proportion of patients achieving PASI50 at week 16. Furthermore, the data showed a reassuring safety profile, with no treatment-related serious adverse events, and no meaningful difference in infection or gastrointestinal events from placebo. Results from this trial suggest the potential of EDP1815 as a safe, effective, oral, and well-tolerated therapy for psoriasis[102].

4. Conclusion

The therapeutic landscape for psoriasis is now reasonably broad with several successful therapeutic strategies available for the treatment of this condition.
However, there are still unfulfilled therapeutic gaps resulting from the limitations of existing therapies, which have paved the way for the identification of new therapeutic approaches.
Biological agents have dramatically changed the therapeutic scenario and contributed to clarify pathogenic aspects leading to the identification of novel targets and thus the development of further therapeutic agents.

5. Expert opinion

Biological agents provide an excellent treatment option for patients with psoriasis, as they offer a highly selective approach with a superior safety profile compared with traditional systemic agents.
Currently approved biologics target extracellular cytokines that are crucial in psoriasis pathogenesis, such as TNF-α (adalimumab, infliximab, certolizumab and etanercept), IL-23 (ustekinumab, guselkumab, tildrakizumab and risankizumab), and IL-17 (secukinumab,

ixekizumab, bimekizumab and brodalumab). Their use has revolutionized the therapeutic landscape of psoriasis but is still hampered by certain limitations.

~~One of these is the costs of manufacturing. In a recent study, the annual treatment cost per PASI75 responder was estimated to vary according to the biologic agents, with brodalumab 210 mg being the cheapest ($48 782$/year) and ustekinumab the most expensive one (87 243$/year).~~

Managing psoriasis presents many challenges, with one of the main ones relating to difficult-to-treat areas, including scalp, nail, palmoplantar and genital regions. These sites are also often burdened with significant psychological and functional impairment. Due to the location and morphological features, topical treatment can often be ineffective and systemic treatment is often required. To date, clinical trials evaluating therapies for the difficult-to-treat areas have been insufficient. A deeper understanding of the genetic and immunological aspects of regional psoriasis, as well as the identification of unique biomarkers, will further guide management decisions and identify the most beneficial treatments for each psoriasis subtype.

The use of biologics may be also limited by long-term loss of efficacy and safety issues, such as an increased rate of infection, such as tuberculosis reactivation or Candida reactivation in case of anti-TNF-α and IL-17 agents, respectively[103].

Another limitation of monoclonal antibodies is related to their immunogenicity as these drugs have an inherent propensity to cause the development of antidrug antibodies, which may only partially explain the reduction of treatment efficacy[104].

Considering all limitations of currently approved biological drugs, it can be perceived how the development of new therapeutic strategies should be encouraged. For instance, the development of nanobodies, such as sonelokimab, could hold considerable advantages. Indeed, these drugs have the potential to combine the strength of small proteins with the properties of monoclonal antibodies. Sonelokimab, similarly to bimekizumab, can target both IL-17A and F, thus blocking one of the most crucial pathways in psoriasis pathogenesis. Dual neutralization of IL-17A and IL-17F has indeed shown in vitro a greater suppression of inflammation compared with IL-17A inhibition alone[105]. On the other hand, due to its smaller size and its molecular nature, sonelokimab is likely to have better tissue penetration and a reduced propensity to immunogenicity, compared to the currently available biologic agents. For these reasons, this new class of agents may hold the promise to enrich the current therapeutic scenario of psoriasis.

Emerging therapeutic strategies in the field of psoriasis are still partially oriented towards a direct or indirect inhibition of the IL-23/Th17 pathway, currently considered the core of the psoriasis pathogenetic paradigm.

Recent advances have shed light on the mechanisms that regulate IL-17A transcription in Th17 cells and have shown that both RORγT and ROCK2 are intracellular mediators necessary for Th17 cell differentiation. Upon these bases, orally administered small molecules antagonizing RORγT and ROCK2 have been developed and tested in psoriasis patients with promising results so far. The inhibition of this newly described molecular pathway could therefore offer selective blockade of IL-23/Th17 signaling, with the advantage of an oral administration. However, it should be considered that since ROCKs play a central role in the organization of the actin cytoskeleton, the perspective of a complete inhibition of these proteins could raise safety concerns.

Furthermore, since psoriasis is characterized by the activation of more than one immune pathway, a different therapeutic approach using agents with broader activity, such as JAKi or H4R antagonists, may be appealing to provide therapeutic benefit across all patient populations. Inhibition of the JAK/STAT pathway showed efficacy in the treatment of inflammatory skin conditions[33]. These drugs have the advantage of simultaneously targeting multiple downstream cytokines involved in psoriasis pathogenesis.

However, data from clinical trials evaluating the use of oral JAK inhibitors in immune-mediated disorders, such as RA, have arisen safety concerns, suggesting a potentially increased risk of class-specific AEs such as infections, venous thromboembolism (VTE), and malignancies[106]. Due to the selective TYK2 blockade allowing the inhibition of key cytokine-mediated signals, such as those induced by IL-12 and IL-23, anti-TYK2 agents appear to be very promising as the safety profile appears as superior compared with pan-JAKi.

Moreover, some of the novel above-mentioned therapeutic strategies seem interesting because of their innovative mode-of-action. HSP90 inhibition, for instance, is currently investigated not only in psoriasis but also in other chronic inflammatory dermatoses, such as hidradenitis suppurativa (NCT05286567). Thus, it could become a key strategy in those patients with psoriasis who concomitantly suffer from hidradenitis suppurativa, though safety profile should be carefully evaluated, given the broad physiological functions of HSP90.

However, in a broad therapeutic landscape such as the one available in psoriasis, future agents will likely need to demonstrate a benefit beyond the clinical efficacy (e.g., cost or ease of use) to ensure clinical adoption. Whether the preliminary results obtained by these new agents will be confirmed in phase III trials, the future scenario for a personalized therapeutic approach, may be based on an armamentarium with a more diversified set of oral and biologic therapies helping physician to tailor therapy.

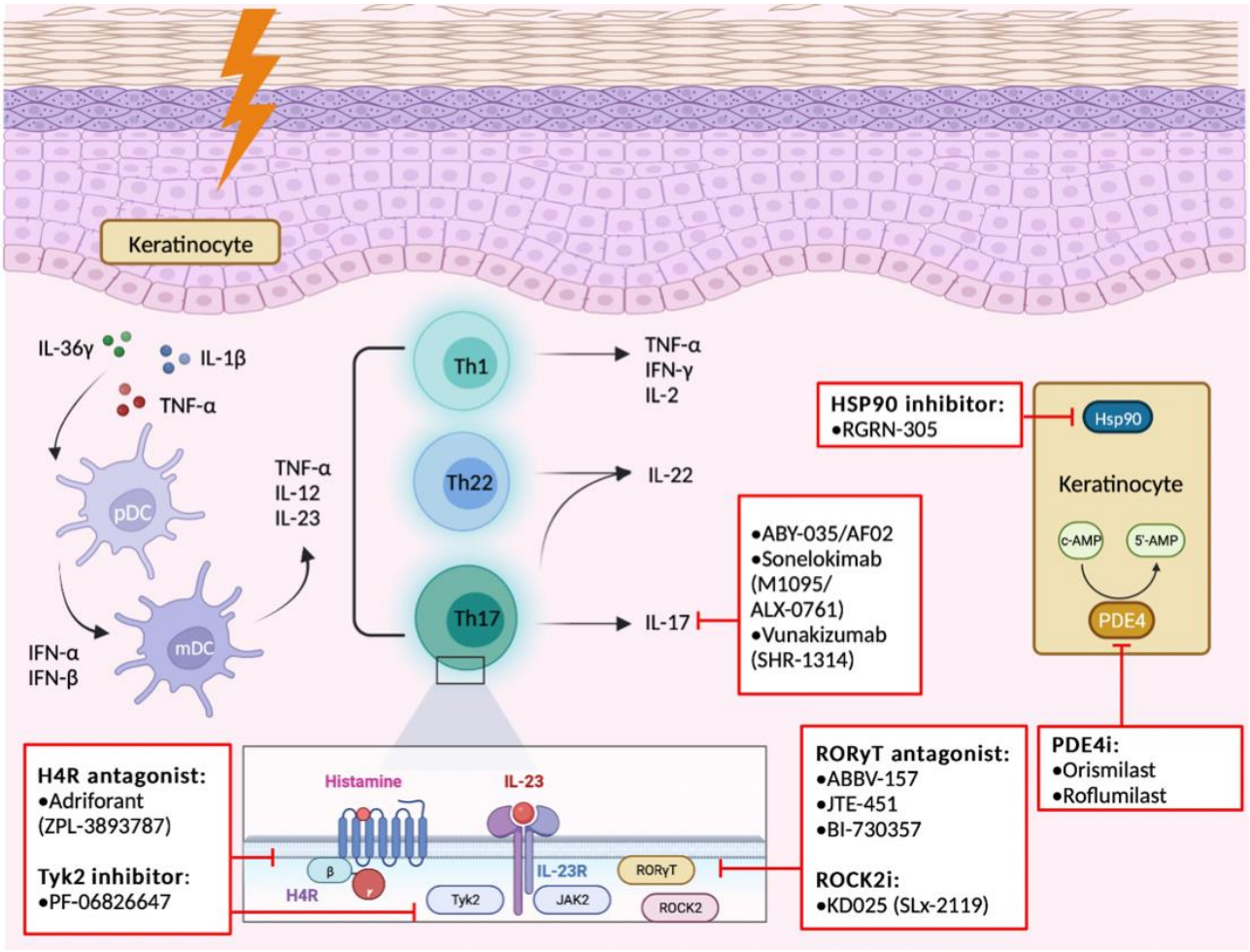

Figure1. Outline of systemic therapeutic strategies in the pipeline for psoriasis and their cellular targets.

Abbreviations: cAMP, cyclic adenosine monophosphate; JAK, Janus kinase; HSP90, Heat Shock Protein 90; H4R, Histamine receptor 4; IL, interleukin; IFN, interferon; PDE4, phosphodiesterase 4; PDE4i, phosphodiesterase 4 inhibitors; Rho-associated coiled-coil–containing protein kinase 2; ROCK2; RORγT, Retinoic acid-related orphan nuclear receptors; TYK2, tyrosine kinase 2; TNF, tumor necrosis factor.

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Table 1. Novel therapeutic agents currently in phase I/II of development for psoriasis vulgaris

		Agent (acronym)	Mode of action	Study Phase	Clinical trial identifier	Pso severity	Study duration	Primary endpoint	Status
Biologics		ABY035/AF02 (Izokibep)	IL-17A inhibitor	Phase II	NCT03591887	Moderate-to-severe	56 weeks	PASI 90 at week 12	Completed
		M1095/ALX-0761 (Sonelokimab)	Anti-IL-17A/F Nanobody	Phase II b	NCT03384745	Moderate-to-severe	52 weeks	IGA 0/1 at week 12	Completed
		SHR-1314 (Vunakizumab)	mAb anti IL-17A	Part A: Phase I	NCT03463187	Moderate-to-severe	24 weeks	N. of participants with clinically significant events	Unknown
				Part B: Phase II	NCT03463187	Moderate-to-severe	36 weeks	PASI 75 at week 12	
		CC-90006	anti-PD-1 agonist antibody	Phase I	NCT03337022	Mild-to moderate	20 weeks	N. of participants with clinically significant adverse events	Completed
		Namilumab	Anti GM-CSF antibody	Phase II	NCT02129777	Moderate-to-severe	52 weeks	PASI 75 at week 12	Completed
		GSK2831781	Anti LAG-3 antibody	Phase I	NCT02195349	Mild-to moderate	Up to 307 days	N. of participants with clinically significant adverse events	Completed
Oral	JAK pathway inhibitor	PF-06826647	TYK2 inhibitor	Phase II	NCT03895372	Moderate-to-severe	16 weeks	PASI 90 at week 16	Completed
	Receptor antagonist	BI-730357	RORγT antagonist	Phase II	NCT03635099	Moderate-to-severe	12 weeks	PASI 75 at week 12; sPGA 0/1 at Week 12	Completed
		JTE-451	RORγT antagonist	Phase II	NCT03832738	Moderate-to-severe	16 weeks	PASI 75 at week 16	Completed
		Cedirogant (ABBV-157)	RORγT antagonist	Phase II	NCT05044234	Moderate-to-severe	16 weeks	PASI 75 at week 16	Active, not recruiting
		Adriforant (ZPL-3893787)	Oral H4R antagonist	Phase II	NCT02618616	Moderate-to-severe	12 weeks	Percent change from Baseline in PASI Index at Week 12	Completed

		CC-92252	IL-2R antagonist	Phase I	NCT03971825	Mild-to moderate	16 weeks	N. of participants with clinically significant adverse events	Terminated
	Serin/threonin kinase inhibitor	Belumosudil (KD025; SLx-2119)	ROCK2 inhibitor	Phase II	NCT02852967	Moderate-to-severe	16 weeks	PASI 75 at week 16	Completed
	Phosphodiesterase 4 inhibitors	Orismilast	PDEA4i	Phase II	NCT05190419	Moderate-to-severe	16 weeks	Percent change from Baseline in PASI Index at Week 16	Active, not recruiting
		Roflumilast	PDEA4i	Phase II	NCT04549870	Moderate-to-severe	12 weeks	PASI 75 at week 12	Active, not recruiting
	Fumaric acid esters	Tepilamide fumarate (PPC-06)	FAEs	Phase II	NCT03421197	Moderate-to-severe	24 weeks	PASI 75 at week 24; sPGA 0/1 at Week 24	Completed
	Heat Shock Protein 90 Inhibition	RGRN-305 (CUDC-305)	HSP90 inhibitor	Phase I	NCT03675542	Mild-to moderate	12 weeks	Change from baseline in PASI score at week 12; Incidence of TEAEs at week 12	Unknown
	Oral microbials	EDP1815	*Prevotella histicola*	Phase II	NCT04603027	Mild-to moderate	16 weeks	Mean percentage change in PASI at week 16	Completed
		EDP1066		Phase I	NCT03542994	Mild-to moderate	60 days	N. of participants with clinically significant adverse events	Completed

Abbreviations: Anti-PD-1, programmed cell death (PD)-1; FAEs; Fumaric acid esters; IL, interleukin; GM-CSF, granulocyte-macrophage colony stimulating factor; HSP90, Heat Shock Protein 90; H4R, Histamine receptor 4; IGA, Investigator's Global assessment; LAG-3, Lymphocyte Activation Gene-3; mAb, monoclonal antibody; PASI, Psoriasis Area Severity Index; PDEA4i, Phosphodiesterase 4 inhibitors; Rho-associated coiled-coil–containing protein kinase 2; ROCK2; RORγT, Retinoic acid-related orphan nuclear receptors; sPGA, Static Physician's Global Assessment Score; TEAEs, treatment-emergent adverse events; TYK2, tyrosine kinase 2.

Reference

1. Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol. 2017 Feb;31(2):205-212.
2. Boehncke WH, Schön MP. Psoriasis. Lancet. 2015 Sep 5;386(9997):983-94.
3. Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. Lancet. 2018 Jun 2;391(10136):2273-2284.
4. Parisi R, Symmons DP, Griffiths CE, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013 Feb;133(2):377-85.
5. Horn EJ, Fox KM, Patel V, et al. Association of patient-reported psoriasis severity with income and employment. J Am Acad Dermatol. 2007 Dec;57(6):963-71.
6. Rendon A, Schakel K. Psoriasis Pathogenesis and Treatment. Int J Mol Sci. 2019 Mar 23;20(6).
7. Nair RP, Stuart PE, Nistor I, et al. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. Am J Hum Genet. 2006 May;78(5):827-851.
8. Gudjonsson JE, Johnston A, Sigmundsdottir H, et al. Immunopathogenic mechanisms in psoriasis. Clin Exp Immunol. 2004 Jan;135(1):1-8.
9. Genetic Analysis of Psoriasis C, the Wellcome Trust Case Control C, Strange A, et al. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nat Genet. 2010 Nov;42(11):985-90.
10. Nair RP, Duffin KC, Helms C, et al. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. Nat Genet. 2009 Feb;41(2):199-204.
11. Griffiths CEM, Armstrong AW, Gudjonsson JE, et al. Psoriasis. Lancet. 2021 Apr 3;397(10281):1301-1315.
12. Arakawa A, Siewert K, Stohr J, et al. Melanocyte antigen triggers autoimmunity in human psoriasis. J Exp Med. 2015 Dec 14;212(13):2203-12.
13. Lande R, Botti E, Jandus C, et al. The antimicrobial peptide LL37 is a T-cell autoantigen in psoriasis. Nat Commun. 2014 Dec 3;5:5621.
14. Valdimarsson H, Baker BS, Jonsdottir I, et al. Psoriasis: a T-cell-mediated autoimmune disease induced by streptococcal superantigens? Immunol Today. 1995 Mar;16(3):145-9.
15. Vignali DA, Kuchroo VK. IL-12 family cytokines: immunological playmakers. Nat Immunol. 2012 Jul 19;13(8):722-8.
16. Nestle FO, Conrad C, Tun-Kyi A, et al. Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. J Exp Med. 2005 Jul 4;202(1):135-43.
17. Trinchieri G, Pflanz S, Kastelein RA. The IL-12 family of heterodimeric cytokines: new players in the regulation of T cell responses. Immunity. 2003 Nov;19(5):641-4.
18. Trinchieri G. Interleukin-12 and the regulation of innate resistance and adaptive immunity. Nat Rev Immunol. 2003 Feb;3(2):133-46.
19. Tang L, Yang X, Liang Y, et al. Transcription Factor Retinoid-Related Orphan Receptor gammat: A Promising Target for the Treatment of Psoriasis. Front Immunol. 2018;9:1210.
20. Ghoreschi K, Balato A, Enerback C, et al. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. Lancet. 2021 Feb 20;397(10275):754-766.
21. Chiricozzi A, Guttman-Yassky E, Suarez-Farinas M, et al. Integrative responses to IL-17 and TNF-alpha in human keratinocytes account for key inflammatory pathogenic circuits in psoriasis. J Invest Dermatol. 2011 Mar;131(3):677-87.
22. Kalliolias GD, Ivashkiv LB. TNF biology, pathogenic mechanisms and emerging therapeutic strategies. Nat Rev Rheumatol. 2016 Jan;12(1):49-62.
23. Brenner D, Blaser H, Mak TW. Regulation of tumour necrosis factor signalling: live or let die. Nat Rev Immunol. 2015 Jun;15(6):362-74.
24. Brembilla NC, Senra L, Boehncke WH. The IL-17 Family of Cytokines in Psoriasis: IL-17A and Beyond. Front Immunol. 2018;9:1682.
25. Di Cesare A, Di Meglio P, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. J Invest Dermatol. 2009 Jun;129(6):1339-50.

26. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med. 2011 Aug 18;365(7):620-8.
27. Calabrese L, Caldarola G, Peris K, et al. Recalcitrant Sweet Syndrome successfully treated with adalimumab. J Dtsch Dermatol Ges. 2021 Jan;19(1):122-124.
28. Morizane S, Yamasaki K, Muhleisen B, et al. Cathelicidin antimicrobial peptide LL-37 in psoriasis enables keratinocyte reactivity against TLR9 ligands. J Invest Dermatol. 2012 Jan;132(1):135-43.
29. Chiricozzi A, Romanelli P, Volpe E, et al. Scanning the Immunopathogenesis of Psoriasis. Int J Mol Sci. 2018 Jan 8;19(1).
30. Banerjee S, Biehl A, Gadina M, et al. JAK-STAT Signaling as a Target for Inflammatory and Autoimmune Diseases: Current and Future Prospects. Drugs. 2017 Apr;77(5):521-546.
31. Shreberk-Hassidim R, Ramot Y, Zlotogorski A. Janus kinase inhibitors in dermatology: A systematic review. J Am Acad Dermatol. 2017 Apr;76(4):745-753 e19.
32. Armstrong AW, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. JAMA. 2020 May 19;323(19):1945-1960.
33. D'Urso DF, Chiricozzi A, Pirro F, et al. New JAK inhibitors for the treatment of psoriasis and psoriatic arthritis. G Ital Dermatol Venereol. 2020 Aug;155(4):411-420.
34. Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis. 2005 Mar;64 Suppl 2(Suppl 2):ii65-8; discussion ii69-73.
35. Bruner CR, Feldman SR, Ventrapragada M, et al. A systematic review of adverse effects associated with topical treatments for psoriasis. Dermatol Online J. 2003 Feb;9(1):2.
36. Ben Abdallah H, Johansen C, Iversen L. Key Signaling Pathways in Psoriasis: Recent Insights from Antipsoriatic Therapeutics. Psoriasis (Auckl). 2021;11:83-97.
37. FDA approval of Remicade (infliximab) for the treatment of psoriasis. Published November 2013 https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103772s5359lbl.pdf. (Accessed 23 November 2022).
38. FDA approval of Humira (adalimumab) for the treatment of psoriasis. Published December 2020 https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125057s417lbl.pdf. (Accessed 23 November 2022).
39. FDA approval of Cimzia (certolizumab) for the treatment of psoriasis. Published April 2016 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125160s270lbl.pdf (Accessed 23 November 2022).
40. FDA approval of Enbrel (etanercept) for the treatment of psoriasis. Published September 2011 https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103795s5503lbl.pdf (Accessed 23 November 2022).
41. Mitoma H, Horiuchi T, Tsukamoto H, et al. Molecular mechanisms of action of anti-TNF-alpha agents - Comparison among therapeutic TNF-alpha antagonists. Cytokine. 2018 Jan;101:56-63.
42. FDA approval of Cosentyx (secukinumab) for the treatment of psoriasis. Published May 2021

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125504s043lbl.pdf (Accessed 23 November 2022).
43. FDA approval of Taltz (ixekizumab) for the treatment of psoriasis. Published December 2017

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125521s004lbl.pdf (Accessed 23 November 2022).
44. FDA approval of Siliq (brodalumab) for the treatment of psoriasis. Published 2017

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761032lbl.pdf (Accessed 23 November 2022).
45. EMA approval of Bimzelx (bimekizumab) for the treatment of psoriasis. Published August 2021

https://www.ema.europa.eu/en/documents/product-information/bimzelx-epar-product-information_en.pdf (Accessed 23 November 2022).
46. FDA approval of Stelara (ustekinumab) for the treatment of psoriasis. Published September 2016

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761044lbl.pdf (Accessed 24 November 2022).
47. FDA approval of Tremfya (guselkumab) for the treatment of psoriasis. Published July 2020

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761061s007lbl.pdf (Accessed 24 November 2022).
48. FDA approval of Ilumya (Tildrakizumab) for the treatment of psoriasis. Published March 2018

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761067s000lbl.pdf (Accessed 24 November 2022).
49. FDA approval of Skyrizi (Risankizumab) for the treatment of psoriasis. Published January 2022

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761105s014lbl.pdf (Accessed 24 November 2022).
50. FDA approval of Otezla (Apremilast) for the treatment of psoriasis. Published June 2017

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205437s006lbl.pdf (Accessed 24 November 2022).
51. Chiricozzi A, Caposiena D, Garofalo V, et al. A new therapeutic for the treatment of moderate-to-severe plaque psoriasis: apremilast. Expert Rev Clin Immunol. 2016;12(3):237-49.
52. Behrens F TP, Wetzel D OP0258 IZOKIBEP (ABY-035) IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS – 16-WEEK RESULTS FROM A PHASE 2 STUDY. Annals of the Rheumatic Diseases. 2022;81:170-171.
53. Sun S, Ding Z, Yang X, et al. Nanobody: A Small Antibody with Big Implications for Tumor Therapeutic Strategy. Int J Nanomedicine. 2021;16:2337-2356.
54. Papp KA, Weinberg MA, Morris A, et al. IL17A/F nanobody sonelokimab in patients with plaque psoriasis: a multicentre, randomised, placebo-controlled, phase 2b study. Lancet. 2021 Apr 24;397(10284):1564-1575.
55. Zhang C, Yan K, Diao Q, et al. A multicenter, randomized, double-blinded, placebo-controlled, dose-ranging study evaluating the efficacy and safety of vunakizumab in patients with moderate-to-severe plaque psoriasis. J Am Acad Dermatol. 2022 Jul;87(1):95-102.
56. Workman CJ, Vignali DA. Negative regulation of T cell homeostasis by lymphocyte activation gene-3 (CD223). J Immunol. 2005 Jan 15;174(2):688-95.
57. Okazaki T, Okazaki IM, Wang J, et al. PD-1 and LAG-3 inhibitory co-receptors act synergistically to prevent autoimmunity in mice. J Exp Med. 2011 Feb 14;208(2):395-407.
58. Wierz M, Pierson S, Guyonnet L, et al. Dual PD1/LAG3 immune checkpoint blockade limits tumor development in a murine model of chronic lymphocytic leukemia. Blood. 2018 Apr 5;131(14):1617-1621.
59. Workman CJ, Rice DS, Dugger KJ, et al. Phenotypic analysis of the murine CD4-related glycoprotein, CD223 (LAG-3). Eur J Immunol. 2002 Aug;32(8):2255-63.
60. Poirier N, Haudebourg T, Brignone C, et al. Antibody-mediated depletion of lymphocyte-activation gene-3 (LAG-3(+))-activated T lymphocytes prevents delayed-type hypersensitivity in non-human primates. Clin Exp Immunol. 2011 May;164(2):265-74.
61. Ellis J, D JBM, Srinivasan N, et al. Depletion of LAG-3(+) T Cells Translated to Pharmacology and Improvement in Psoriasis Disease Activity: A Phase I Randomized Study of mAb GSK2831781. Clin Pharmacol Ther. 2021 May;109(5):1293-1303.
62. Curnock AP, Bossi G, Kumaran J, et al. Cell-targeted PD-1 agonists that mimic PD-L1 are potent T cell inhibitors. JCI Insight. 2021 Oct 22;6(20).
63. Papp KA, Gooderham M, Jenkins R, et al. Granulocyte-macrophage colony-stimulating factor (GM-CSF) as a therapeutic target in psoriasis: randomized, controlled investigation using namilumab, a specific human anti-GM-CSF monoclonal antibody. Br J Dermatol. 2019 Jun;180(6):1352-1360.
64. Krueger JG, McInnes IB, Blauvelt A. Tyrosine kinase 2 and Janus kinase–signal transducer and activator of transcription signaling and inhibition in plaque psoriasis. J Am Acad Dermatol. 2022 Jan;86(1):148-157.
65. Tehlirian C, Singh RSP, Pradhan V, et al. Oral tyrosine kinase 2 inhibitor PF-06826647 demonstrates efficacy and an acceptable safety profile in participants with moderate-to-severe plaque psoriasis in a phase 2b, randomized, double-blind, placebo-controlled study. J Am Acad Dermatol. 2022 Aug;87(2):333-342.

66. Gege C. Retinoic acid-related orphan receptor gamma t (RORgammat) inverse agonists/antagonists for the treatment of inflammatory diseases - where are we presently? Expert Opin Drug Discov. 2021 Dec;16(12):1517-1535.
67. Haggerty HG, Sathish JG, Gleason CR, et al. Thymic Lymphomas in a 6-Month rasH2-Tg Mouse Carcinogenicity Study With the RORgammat Inverse Agonist, BMS-986251. Toxicol Sci. 2021 Aug 30;183(1):93-104.
68. Vitae Pharmaceuticals, 8-K - Current report, published: 2016-Mar16. [cited 2021 Mar 15]. Available from: https://sec.report/Document/0001104659-16-105501/.
69. Zampeli E, Tiligada E. The role of histamine H4 receptor in immune and inflammatory disorders. Br J Pharmacol. 2009 May;157(1):24-33.
70. Alcain J, Infante Cruz ADP, Barrientos G, et al. Mechanisms of unconventional CD8 Tc2 lymphocyte induction in allergic contact dermatitis: Role of H(3)/H(4) histamine receptors. Front Immunol. 2022;13:999852.
71. Han SH, Hur MS, Kim MJ, et al. Preliminary study of histamine H(4) receptor expressed on human CD4(+) T cells and its immunomodulatory potency in the IL-17 pathway of psoriasis. J Dermatol Sci. 2017 Oct;88(1):29-35.
72. Taniguchi T, Matsui H, Fujita T, et al. Structure and expression of a cloned cDNA for human interleukin-2. Nature. 1983 Mar 24-30;302(5906):305-10.
73. Abbas AK, Trotta E, D RS, et al. Revisiting IL-2: Biology and therapeutic prospects. Sci Immunol. 2018 Jul 6;3(25).
74. Lugnier C. Cyclic nucleotide phosphodiesterase (PDE) superfamily: a new target for the development of specific therapeutic agents. Pharmacol Ther. 2006 Mar;109(3):366-98.
75. Li H, Zuo J, Tang W. Phosphodiesterase-4 Inhibitors for the Treatment of Inflammatory Diseases. Front Pharmacol. 2018;9:1048.
76. Maurice DH, Ke H, Ahmad F, et al. Advances in targeting cyclic nucleotide phosphodiesterases. Nat Rev Drug Discov. 2014 Apr;13(4):290-314.
77. Strober B, Alikhan A, Lockshin B, et al. Apremilast mechanism of efficacy in systemic-naive patients with moderate plaque psoriasis: Pharmacodynamic results from the UNVEIL study. J Dermatol Sci. 2019 Dec;96(3):126-133.
78. Garcet S, Nograles K, Correa da Rosa J, et al. Synergistic cytokine effects as apremilast response predictors in patients with psoriasis. J Allergy Clin Immunol. 2018 Sep;142(3):1010-1013 e6.
79. Lebwohl MG, Papp KA, Stein Gold L, et al. Trial of Roflumilast Cream for Chronic Plaque Psoriasis. N Engl J Med. 2020 Jul 16;383(3):229-239.
80. Hennig P, Fenini G, Di Filippo M, et al. Electrophiles Against (Skin) Diseases: More Than Nrf2. Biomolecules. 2020 Feb 11;10(2).
81. Kobayashi EH, Suzuki T, Funayama R, et al. Nrf2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription. Nat Commun. 2016 May 23;7:11624.
82. Kastrati I, Siklos MI, Calderon-Gierszal EL, et al. Dimethyl Fumarate Inhibits the Nuclear Factor kappaB Pathway in Breast Cancer Cells by Covalent Modification of p65 Protein. J Biol Chem. 2016 Feb 12;291(7):3639-47.
83. EMA approval of Skilarence (dimethyl fumarate) for the treatment of psoriasis. Published June 2017

Skilarence, INN-dimethyl fumarate (europa.eu) (Accessed 24 November 2022).
84. Mrowietz U, Kircik L, Reich K, et al. Tepilamide Fumarate (PPC-06) Extended Release Tablets in Patients with Moderate-to-Severe Plaque Psoriasis: Safety and Efficacy Results from the Randomized, Double-blind, Placebo-controlled AFFIRM Study. J Clin Aesthet Dermatol. 2022 Jan;15(1):53-58.
85. Mrowietz U, Christophers E, Altmeyer P. Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. German Multicentre Study. Br J Dermatol. 1998 Mar;138(3):456-60.
86. Mrowietz U, Szepietowski JC, Loewe R, et al. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm((R)) - and placebo-controlled trial (BRIDGE). Br J Dermatol. 2017 Mar;176(3):615-623.
87. Riento K, Ridley AJ. Rocks: multifunctional kinases in cell behaviour. Nat Rev Mol Cell Biol. 2003 Jun;4(6):446-56.

88. Biswas PS, Gupta S, Chang E, et al. Phosphorylation of IRF4 by ROCK2 regulates IL-17 and IL-21 production and the development of autoimmunity in mice. J Clin Invest. 2010 Sep;120(9):3280-95.
89. Weiss JM, Chen W, Nyuydzefe MS, et al. ROCK2 signaling is required to induce a subset of T follicular helper cells through opposing effects on STATs in autoimmune settings. Sci Signal. 2016 Jul 19;9(437):ra73.
90. Zanin-Zhorov A, Weiss JM, Nyuydzefe MS, et al. Selective oral ROCK2 inhibitor down-regulates IL-21 and IL-17 secretion in human T cells via STAT3-dependent mechanism. Proc Natl Acad Sci U S A. 2014 Nov 25;111(47):16814-9.
91. Zanin-Zhorov A, Weiss JM, Trzeciak A, et al. Cutting Edge: Selective Oral ROCK2 Inhibitor Reduces Clinical Scores in Patients with Psoriasis Vulgaris and Normalizes Skin Pathology via Concurrent Regulation of IL-17 and IL-10. J Immunol. 2017 May 15;198(10):3809-3814.
92. Edwards MJ, Marks R, Dykes PJ, et al. Heat shock proteins in cultured human keratinocytes and fibroblasts. J Invest Dermatol. 1991 Mar;96(3):392-6.
93. Tukaj S, Zillikens D, Kasperkiewicz M. Inhibitory effects of heat shock protein 90 blockade on proinflammatory human Th1 and Th17 cell subpopulations. J Inflamm (Lond). 2014 Apr 2;11(1):10.
94. Kumar P, Kolls JK. Act1-hsp90 heats up TH17 inflammation. Nat Immunol. 2013 Jan;14(1):16-7.
95. Prinsloo E, Kramer AH, Edkins AL, et al. STAT3 interacts directly with Hsp90. IUBMB Life. 2012 Mar;64(3):266-73.
96. Kakeda M, Arock M, Schlapbach C, et al. Increased expression of heat shock protein 90 in keratinocytes and mast cells in patients with psoriasis. J Am Acad Dermatol. 2014 Apr;70(4):683-690 e1.
97. Zhou Z, Li X, Qian Y, et al. Heat shock protein 90 inhibitors suppress pyroptosis in THP-1 cells. Biochem J. 2020 Oct 30;477(20):3923-3934.
98. Carlstrom M, Ekman AK, Petersson S, et al. Genetic support for the role of the NLRP3 inflammasome in psoriasis susceptibility. Exp Dermatol. 2012 Dec;21(12):932-7.
99. Hansen RS, Thuesen KKH, Bregnhoj A, et al. The HSP90 inhibitor RGRN-305 exhibits strong immunomodulatory effects in human keratinocytes. Exp Dermatol. 2021 Jun;30(6):773-781.
100. Stenderup K, Rosada C, Gavillet B, et al. Debio 0932, a new oral Hsp90 inhibitor, alleviates psoriasis in a xenograft transplantation model. Acta Derm Venereol. 2014 Nov;94(6):672-6.
101. Bregnhoj A, Thuesen KKH, Emmanuel T, et al. HSP90 inhibitor RGRN-305 for oral treatment of plaque-type psoriasis: efficacy, safety and biomarker results in an open-label proof-of-concept study. Br J Dermatol. 2022 May;186(5):861-874.
102. Evelo Biosciences presents late-breaking oral abstract on data from phase 2 trial of EDP1815 in psoriasis at 2022 American Academy of Dermatology Annual Meeting. Evelo Biosciences. Press release. Published March 26, 2022. Accessed December 3, 2022. https://ir.evelobio.com/news-releases/news-release-details/evelo-biosciences-presents-late-breaking-oral-abstract-data/.
103. Siegel SAR, Winthrop KL. In the Real World: Infections Associated with Biologic and Small Molecule Therapies in Psoriatic Arthritis and Psoriasis. Curr Rheumatol Rep. 2019 Jun 6;21(7):36.
104. Hsu L, Snodgrass BT, Armstrong AW. Antidrug antibodies in psoriasis: a systematic review. Br J Dermatol. 2014 Feb;170(2):261-73.
105. Glatt S, Baeten D, Baker T, et al. Dual IL-17A and IL-17F neutralisation by bimekizumab in psoriatic arthritis: evidence from preclinical experiments and a randomised placebo-controlled clinical trial that IL-17F contributes to human chronic tissue inflammation. Ann Rheum Dis. 2018 Apr;77(4):523-532.
106. Harrington R, Al Nokhatha SA, Conway R. JAK Inhibitors in Rheumatoid Arthritis: An Evidence-Based Review on the Emerging Clinical Data. J Inflamm Res. 2020;13:519-531.