Expanding the Psoriasis Framework: Immunopathogenesis and Treatment Updates

Yvonne Nong, MD, MS; George Han, MD, PhD; Jason E. Hawkes, MD, MS

PRACTICE **POINTS**

- Psoriasis is a chronic inflammatory condition characterized by systemic inflammation and dysregulated IL-23/IL-17 signaling.
- Modern discoveries highlight the role of additional immune signals in psoriatic disease such as IL-17C, IL-17F, IL-36, and tyrosine kinase 2, which also contribute to disease development.
- Novel systemic, oral, and topical therapies have become available and add to the rapidly growing armamentarium of safe and effective treatments for psoriatic disease.

Psoriasis is a chronic heterogeneous condition with multiple available treatment options that have resulted in dramatic disease improvements for patients. IL-23/IL-17 signaling is the central immune signaling pathway driving psoriasis, though recent research has uncovered other key contributing signals such as IL-17C, IL-17F, IL-36, and tyrosine kinase 2 (TYK2). Novel therapeutic targets inhibiting these cytokines have expanded our understanding of the pathogenesis of psoriasis. IL-23/IL-17 signaling is critical for the development of epidermal hyperplasia and the mature psoriatic plaque in susceptible individuals. Increased IL-17 and IL-23 expression works synergistically with other cytokines, such as IL-12, IL-22, IL-36, tumor necrosis factor (TNF), and interferon (IFN), to help create a self-sustaining, feed-forward circuit in keratinocytes, which contributes to the chronicity of the disease. This clinical review highlights recent discoveries in the immunopathogenesis of psoriasis and summarizes new antipsoriasis therapies targeting IL-36, IL-17F, aryl hydrocarbon receptors (AHRs), phosphodiesterase 4 (PDE4), and TYK2 signaling. Despite recent success in the treatment of psoriasis, continued research is needed to further advance disease understanding and shape management strategies.

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Psoriasis is a chronic inflammatory disease that affects approximately 3% of the US population.[1] Plaque psoriasis comprises 80% to 90% of cases, while pustular, erythrodermic, guttate, inverse, and palmoplantar disease are less common variants (Figure 1). Psoriatic skin manifestations range from localized to widespread or generalized disease with recurrent flares. Body surface area or psoriasis area and severity index (PASI) measurements primarily focus on skin manifestations and are important for evaluating disease activity and

Dr. Nong is from the Department of Internal Medicine, SUNY Downstate Medical Center, Brooklyn, New York. Dr. Nong also is from and Dr. Hawkes is from Integrative Skin Science and Research, Pacific Skin Institute, Sacramento, California. Dr. Han is from the Department of Dermatology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New Hyde Park, New York.

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The eTable is in the Appendix online at www.mdedge.com/dermatology.

Correspondence: Jason E. Hawkes, MD, MS, Integrative Skin Science and Research, Pacific Skin Institute, 1495 River Park Dr, Sacramento, CA 95815 (hawkes3@gmail.com).

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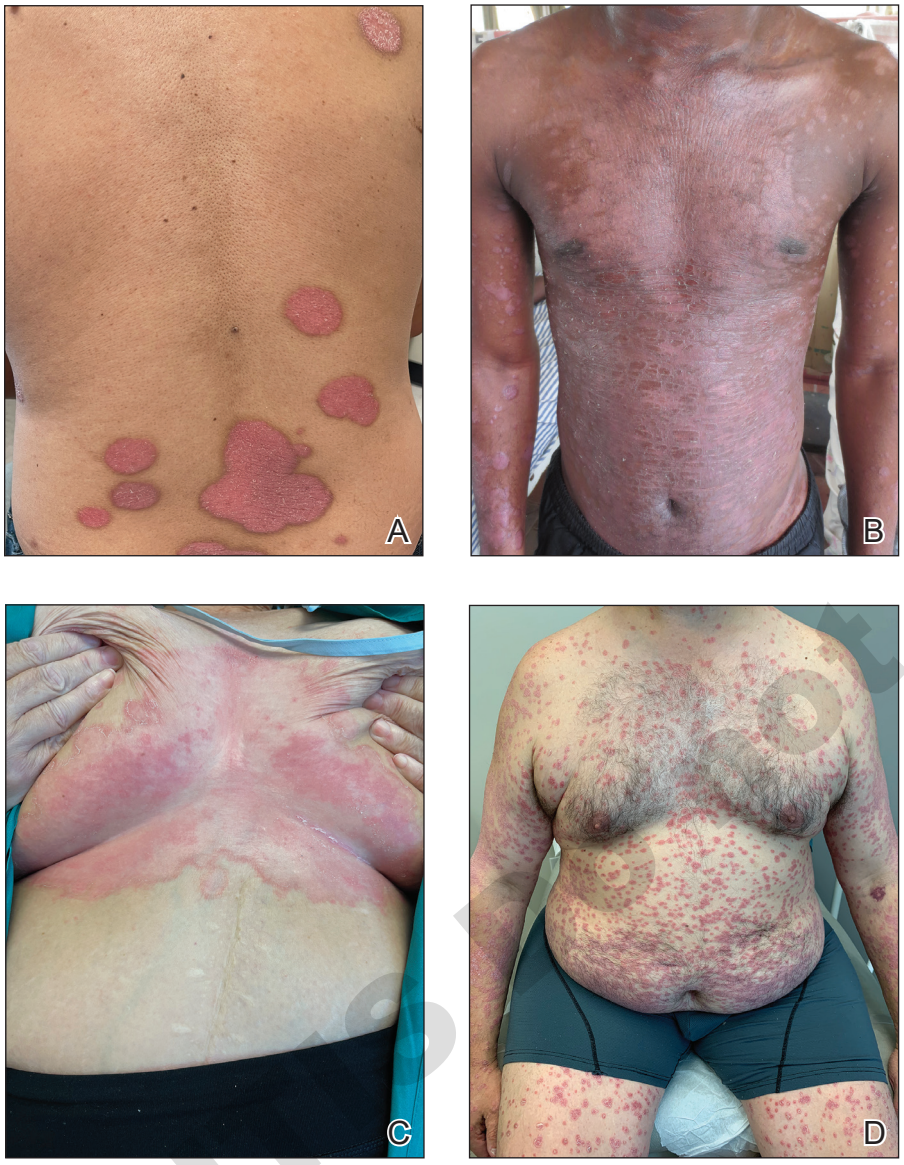

FIGURE 1. A and B, Characteristic plaque psoriasis of the trunk. C, Inverse psoriasis involving the inframammary folds. D, Guttate psoriasis in an adult following streptococcal infection.

response to treatment, but they have inherent limitations: they do not capture extracutaneous disease activity, systemic inflammation, comorbid conditions, quality of life impact, or the economic burden of psoriasis.

A common manifestation of psoriasis is psoriatic arthritis (PsA), which can involve the nails, joints, ligaments, or tendons in 30% to 41% of affected individuals (Figure 2).[2,3] A growing number of psoriasis-associated comorbidities also have been reported including metabolic syndrome[4]; hyperlipidemia[5]; cardiovascular disease[6]; stroke[7]; hypertension[8]; obesity[9]; sleep disorders[10]; malignancy[11]; infections[12]; inflammatory bowel disease[13]; and mental health disorders such as depression,[14] anxiety,[15] and suicidal ideation.[15] Psoriatic disease also interferes with daily life activities and a patient's overall quality of life, including interpersonal relationships, intimacy, employment, and work productivity.[16] Finally, the total estimated cost of psoriasis-related health care is more than $35 billion annually,[17] representing a substantial economic burden to our health care system and individual patients.

The overall burden of psoriatic disease has declined markedly in the last 2 decades due to revolutionary advances in our understanding of the immunopathogenesis of psoriasis and the subsequent development of improved therapies that predominantly interrupt IL-23/IL-17 cytokine signaling; however, critical knowledge and treatment gaps persist, underscoring the importance of ongoing clinical and research efforts in psoriatic disease. We review the working immune model of psoriasis, summarize related immune discoveries, and highlight recent therapeutic innovations that are shaping psoriatic disease management.

Current Immune Model of Psoriatic Disease

Psoriasis is an autoinflammatory T cell–mediated disease with negligible contributions from the humoral immune

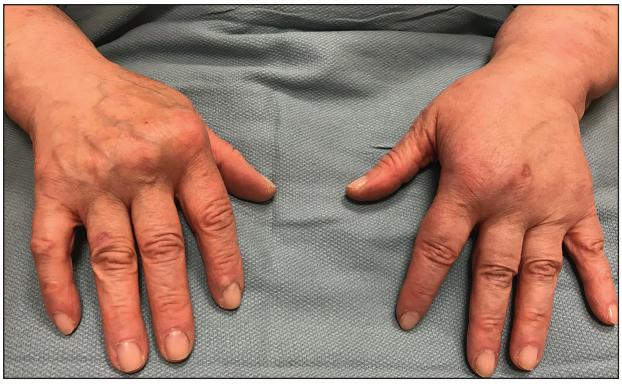

FIGURE 2. Clinical manifestation of psoriatic arthritis involving the metacarpal joints of the hands.

response. Early clinical observations reported increased inflammatory infiltrates in psoriatic skin lesions primarily consisting of both $CD4^+$ and $CD8^+$ T-cell populations.[18,19] Additionally, patients treated with broad-acting, systemic immunosuppressive medications (eg, cyclosporine, oral corticosteroids) experienced improvement of psoriatic lesions and normalization of the immune infiltrates observed in skin biopsy specimens.[20,21] These early clinical findings led to more sophisticated experimentation in xenotransplant models of psoriasis,[22,23] which explored the clinical efficacy of several less immunosuppressive (eg, methotrexate, anti–tumor necrosis factor [TNF] biologics)[24] or T cell–specific agents (eg, alefacept, abatacept, efalizumab).[25-27] The results of these translational studies provided indisputable evidence for the role of the dysregulated immune response as the primary pathogenic process driving plaque formation; they also led to a paradigm shift in how the immunopathogenesis of psoriatic disease was viewed and paved the way for the identification and targeting of other specific proinflammatory signals produced by activated dendritic cell (DC) and T-lymphocyte populations. Among the psoriasis-associated cytokines subsequently identified and studied, elevated IL-23 and IL-17 cytokine levels in psoriatic skin were most closely associated with disease activity, and rapid normalization of IL-23/IL-17 signaling in response to effective oral or injectable antipsoriatic treatments was the hallmark of skin clearance.[28] The predominant role of IL-23/IL-17 signaling in the development and maintenance of psoriatic disease is the central feature of all working immune models for this disease (Figure 3).

Psoriasis-Associated Genetic and Environmental Risk Factors

The exact sequence of events that lead to the initiation and formation of plaque psoriasis in susceptible individuals is still poorly understood; however, several important risk factors and key immune events have been identified. First, decades of genetic research have reported more than 80 known psoriasis-associated susceptibility loci,[29] which explains approximately 50% of psoriasis heritability. The major genetic determinant of psoriasis, HLA-C*06:02 (formerly HLA-Cw6), resides in the major histocompatibility complex class I region on chromosome 6p21.3 (psoriasis susceptibility gene 1, *PSORS1*) and is most strongly associated with psoriatic disease.[30] Less common psoriasis-associated susceptibility genes also are known to directly or indirectly impact innate and adaptive immune functions that contribute to the pathogenesis of psoriasis.

Second, several nongenetic environmental risk factors for psoriasis have been reported across diverse patient populations, including skin trauma/injury, infections, alcohol/tobacco use, obesity, medication exposure (eg, lithium, antimalarials, beta-blockers), and stress.[31] These genetic and/or environmental risk factors can trigger the onset of psoriatic disease at any stage of life, though most patients develop disease in early adulthood or later (age range, 50–60 years). Some patients never develop psoriasis despite exposure to environmental risk factors and/or a genetic makeup that is similar to affected first-degree relatives, which requires further study.

Prepsoriatic Skin and Initiation of Plaque Development

In response to environmental stimuli and/or other triggers of the immune system, DC and resident IL-17–producing T-cell (T17) populations become activated in predisposed individuals. Dendritic cell activation leads to the upregulation and increase of several proinflammatory cytokines, including TNF, interferon (IFN) α, IFN-γ, IL-12, and IL-23. Tumor necrosis factor and IL-23 play a vital role in psoriasis by helping to regulate the polarization and expansion of T22 and T17 cells in the skin, whereas IL-12 promotes a corresponding type 1 inflammatory response.[32] Increased IL-17 and IL-22 result in alteration of the terminal differentiation and proliferative potential of epidermal keratinocytes, leading to the early clinical hallmarks of psoriatic plaques. The potential contribution of overexpressed psoriasis-related autoantigens, such as LL-37/cathelicidin, ADAMTSL5, and PLA2G4D,[33] in the initiation of psoriatic plaques has been suggested but is poorly characterized.[34] Whether these specific autoantigens or others presented by HLA-C variants found on antigen-presenting cells are required for the breakdown of immune tolerance and psoriatic disease initiation is highly relevant but requires further investigation and validation.

Feed-Forward Inflammation, Mature Psoriatic Plaques, and Resident Memory T Cells

In response to the upstream production of IL-23 by dermal DCs, high levels of IL-17 cytokines can be found in mature psoriatic plaques. The IL-17 family consists of 6 dimeric cytokines (IL-17A through IL-17F) that provide innate cutaneous protection against bacterial, viral, and fungal infectious agents, such as *Candida albicans.* Unlike other IL-17 isoforms, IL-17A and IL-17F share the same

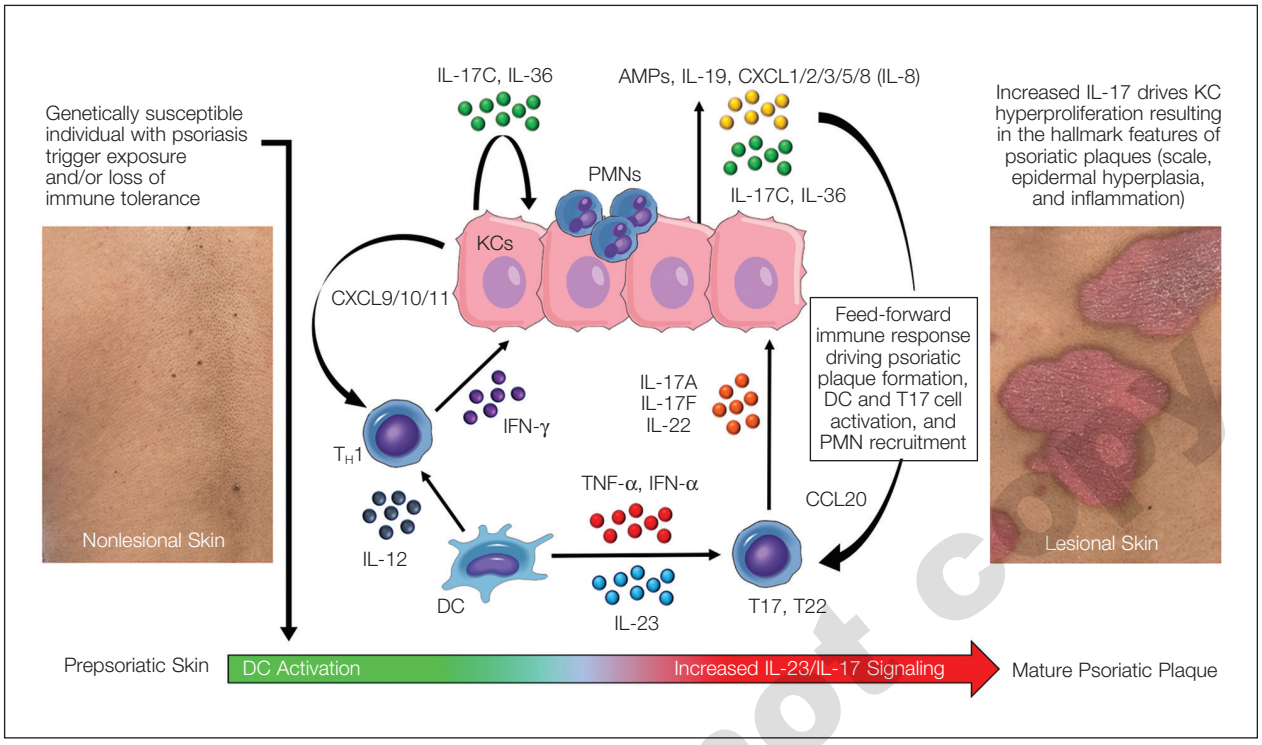

FIGURE 3. Working immune model of psoriasis. Early immune events include activation of dendritic cells (DCs) and IL-17–producing T cells (T17) in the prepsoriatic (or normal-appearing) skin of individuals who are genetically susceptible and/or have exposures to known psoriasis triggers. Activation of DC and T17 populations in the skin results in increased production of tumor necrosis factor (TNF), IL-23, and IL-17 cytokines (namely IL-17A and IL-17F), which work synergistically with other immune signals (IL-12, IL-22, IL-36, TNF, interferon [IFN]) to drive keratinocyte (KC) hyperproliferation. In response to upregulated IL-17 signaling, substantial increases in keratinocyte-derived proteins (antimicrobial peptides, IL-19, IL-36, IL-17C) and chemotactic factors (chemokine [C-C motif] ligand 20 [CCL20], chemokine [C-C motif] ligand 1/2/3/5/8 [CXCL1/2/3/5/8][or IL-8]) facilitate further activation and recruitment of T17 and helper T cell (T_H1) lymphocytes, DCs, macrophages, and polymorphonuclear neutrophils (PMNs) into the skin. The resultant inflammatory circuit creates a self-amplifying or feed-forward immune response in the skin that leads to the hallmark clinical features of psoriasis and sustains the mature psoriatic plaque.

receptor complex and have the highest structural homology of any pair (approximately 50% similar).[35] The relative expression of IL-17F is higher than IL-17A in psoriasis,[36] though IL-17A has been considered as the predominant IL-17 cytokine found in psoriatic skin lesions due to its higher potency.

Binding of IL-17A/F with the IL-17 receptor (IL-17R) on keratinocytes contributes to the development of psoriatic plaques by inducing epidermal hyperplasia via activation of CCAAT/enhancer-binding proteins β and δ, nuclear factor κB, and signal transducer and activator of transcription 1 gene (*STAT1*).[37,38] This also increases the expression of other keratinocyte-derived proteins (eg, human β-defensins, S-100 proteins, LL-37, other antimicrobial peptides, IL-19, IL-36, IL-17C) that act as reinforcing proinflammatory signals or chemotactic factors (eg, chemokine [C-C motif] ligand 20 [CCL20], chemokine [C-C motif] ligand 1/2/3/5 [CXCL1/2/3/5], CXCL8, IL-8) that facilitate the recruitment of additional immune cells to the skin including polymorphonuclear neutrophils (PMNs), macrophages, and DCs.[39-41] Routine immunohistochemical staining for these keratinocyte-derived proteins reveals a striking epidermal gene expression gradient wherein levels of IL-17–induced proteins are most highly expressed in the uppermost layers of keratinocytes and facilitate the recruitment of immune cells into the epidermis. Activated T17 cells also stimulate the production of keratinocyte-derived chemokines (eg, CXCL9/10/11), which recruit type 1 inflammatory T-cell populations into developing psoriatic plaques.[42,43] Finally, TNF, IL-36, and IL-17C cytokines act synergistically with IL-17A/F to amplify the proinflammatory effects of IL-17 signaling and further stimulate their production from T17 cell populations.[40] This inflammatory circuit in the skin creates and supports a self-amplifying or positive feedback loop between the skin and immune system that commonly is referred to as feed-forward inflammation (Figure 3).[34] The feed-forward inflammatory loop in psoriasis—predominantly driven by increased IL-23/IL-17 signaling—best characterizes the mature psoriatic plaque.

Several findings suggest that the influx of persistent, long-lived resident memory T cells (Trms) may contribute to the mature psoriatic plaque. It is believed that $CD8^+CD103^+CD49a^-$ Trm cell populations may be responsible for the sharply demarcated borders of untreated psoriasis plaques or their recurrence at specific

body sites such as the scalp, buttocks, extremity extensor surfaces, umbilicus, or acral skin following specific stimuli or trauma (Koebner phenomenon or isomorphic response).[44,45] It is not known if repeated stimuli or trauma induce disease formation via the activation of Trm cell populations; further study in large patient cohorts is needed, but this remains an intriguing area of study for durable treatment responses and potential cures for psoriasis.

Recent Discoveries in Psoriatic Disease

Remarkable treatment outcomes for psoriasis have been achieved with multiple selective IL-17 and IL-23 inhibitors (eTable). As demonstrated in several pivotal phase 3 clinical trials for members of these classes of medications, the majority of treated psoriasis patients achieved PASI90 clearance.[46] Due to their more favorable dosing schedule (ie, fewer injections) and ability to induce a durable remissionlike treatment response, IL-23 inhibitors have become the preferred treatment class for cutaneous disease, while IL-17 inhibitors may be preferred when treating patients with both plaque psoriasis and PsA.[47,48] Nevertheless, the complexity of this disease is punctuated by treated patients who do not adequately respond to selective IL-23/IL-17 blockade.[49] Recent and emerging treatments may shed light on these recalcitrant cases and will add to the rapidly growing arsenal of available psoriasis therapies.

The Role of IL-17F in Psoriasis and Other Inflammatory Skin Diseases

Dysregulation of IL-17A and IL-17F is associated with several chronic inflammatory conditions, such as psoriasis and PsA.[35,50] Both cytokines, either as homodimers or heterodimers, can selectively bind to the heterodimeric IL-17R formed by the IL-17RA and IL-17RC subunits.[35] IL-17F and IL-17C also can synergize with TNF and other cytokines to promote and support the self-sustaining inflammatory circuits in mature psoriatic plaques, though their inflammatory effects in the skin are more limited than IL-17A.[51,52] Therefore, incomplete blockade of IL-17 signaling (ie, unopposed IL-17F and IL-17C) represents a potential mechanism to explain the persistence of psoriasis in patients treated with selective IL-17A inhibitors. This hypothesis is supported by reports of psoriasis patients who have inadequate clinical responses to selective IL-17A inhibition but subsequently improve with IL-17R blockade, which results in disruption of IL-17A as well as IL-17C/E/F cytokine signaling. This formed the basis for further study into the specific role of IL-17F in psoriatic disease and any potential therapeutic benefits associated with its inhibition.

Recently approved in the European Union, Canada, Australia, Japan, the United Kingdom, and the United States for moderate to severe psoriasis, bimekizumab is a novel humanized IgG antibody that selectively inhibits both IL-17A and IL-17F cytokines.[53] Specifically, bimekizumab simultaneously prevents binding of IL-17A/A, IL-17A/F, and IL-17F/F dimers with the IL-17R. Compared to other IL-17 and IL-23 biologic therapies, bimekizumab (320 mg) achieved relatively higher response rates for PASI75, PASI90, and PASI100.[49] Neutralization of IL-17A and IL-17F by bimekizumab also resulted in more complete suppression of cytokine responses and PMN chemotaxis than either cytokine alone in treated PsA patients,[54] which is notable because of the incremental benefits of recent IL-23 and IL-17 inhibitors on inflammatory arthritis symptoms in contrast to the substantial improvements observed for cutaneous disease with those same agents.

The primary disadvantage of bimekizumab and its more complete blockade of the IL-17 signaling pathway is that treated patients have a substantially increased risk for oral candidiasis (>10%).[55] However, the precise link between candidiasis and IL-17 blockade is not yet fully understood because other targeted agents that also broadly suppress IL-17 signaling (ie, IL-17R, IL-23 inhibitors) are associated with much lower rates of candidiasis.[56-58] Bimekizumab also is being investigated as a novel therapy for hidradenitis suppurativa and will provide important reference information regarding the role for bispecific biologic agents in the treatment of chronic inflammatory skin diseases.[59]

IL-36 Signaling and Generalized Pustular Psoriasis

Recent genetic and clinical studies have expanded our understanding of the role of IL-36 signaling in the immunopathogenesis of pustular psoriasis variants. Generalized pustular psoriasis (GPP) is a rare distinct psoriasis subtype characterized by the recurrent development of widespread erythema, superficial sterile pustules, and desquamation. Systemic symptoms such as fever, malaise, itching, and skin pain accompany acute GPP flares.[60] Generalized pustular psoriasis is more common in female patients (in contrast with plaque psoriasis), and acute flares may be caused by multiple stimuli including infections, hypocalcemia, initiation or discontinuation of medications (eg, oral corticosteroids), pregnancy, or stress.[61,62] Flares of GPP often require emergency or inpatient care, as untreated symptoms increase the risk for severe health complications such as secondary infections, sepsis, or multisystem organ failure.[63] The prevalence of GPP is estimated to be approximately 1 in 10,000 individuals in the United States,[64-67] with mortality rates ranging from 0 to 3.3 deaths per 100 patient-years.[67]

In contrast to plaque psoriasis, aberrant IL-36 signaling is the predominant driver of GPP. IL-36 is a member of the IL-1 cytokine family that includes three IL-36 agonists (IL-36α, IL-36β, IL-36γ) and 1 endogenous antagonist (IL-36Ra, encoded by *IL36RN*).[68] The immunopathogenesis of GPP involves dysregulation of the IL-36–chemokine–PMN axis, resulting in unopposed IL-36 signaling and the subsequent recruitment and influx of

PMNs into the epidermis. *IL36RN* mutations are strongly associated with GPP and result in impaired function of the IL-36Ra protein, leading to unopposed IL-36 signaling.[69] However, approximately two-thirds of GPP patients lack identifiable gene mutations, suggesting other immune mechanisms or triggers causing upregulated IL-36 signaling.[70] In response to these triggers, increased IL-36 cytokines released by keratinocytes bind to the IL-36R, resulting in substantial keratinocyte hyperproliferation, increased IL-36 levels, and the expression of hundreds of additional inflammatory signals (eg, IL-17C, antimicrobial peptides, TNF, IL-6).[71] Increased IL-36 levels also drive the production of PMN chemotactic proteins (eg, CXCL1/2/3/5/6/8 and CXCR1/2) and act synergistically with IL-17 cytokines to create an autoamplifying circuit that is analogous to the feed-forward inflammatory loop in plaque psoriasis.[72] Biopsies of involved GPP skin reveal increased expression of IL-36 in the uppermost layers of the epidermis, which creates a gene expression gradient that acts as a strong attractant for PMNs and forms the basis for the hallmark pustular lesions observed in GPP patients.

Until recently, treatment strategies for GPP involved the off-label use of topical, oral, or biologic therapies approved for plaque psoriasis, which often was associated with variable or incomplete disease control. In September 2022, the US Food and Drug Administration (FDA) approved intravenous spesolimab as a first-in-class humanized monoclonal IgG1 antibody for the treatment of GPP flares in adults. Spesolimab binds to IL-36R and prevents its activation by its endogenous agonists. A phase 2, randomized, 12-week clinical trial (Effisayil-1) evaluated the efficacy and safety of a single 900-mg intravenous dose of spesolimab followed by an optional second dose 1 week later for inadequate treatment responses in 53 enrolled GPP patients (2:1 treatment to placebo randomization).[73] Remarkably, more than half (19/35 [54%]) of GPP patients experienced complete resolution of pustules (GPP physician global assessment subscore of 0 [range, 0–4]) and showed sustained efficacy out to week 12 after just 1 or 2 doses of spesolimab. Overall, the safety profile of spesolimab was good; asthenia, fatigue, nausea, vomiting, headache, pruritus, infusion-related reaction and symptoms, and mild infections (eg, urinary tract infection) were the most common adverse events reported.[73]

Imsidolimab, a high-affinity humanized IgG4 monoclonal antibody that binds and blocks activation of IL-36R, also has completed phase 2 testing,[74] with phase 3 study results expected in early 2024. The rapid onset of action and overall safety of imsidolimab was in line with and similar to spesolimab. Future approval of imsidolimab would add to the limited treatment options available for GPP and has the additional convenience of being administered to patients subcutaneously. Overall, the development of selective IL-36R inhibitors offers a much-needed therapeutic option for GPP and illustrates the importance of translational research.

Role of Tyrosine Kinase in Psoriatic Disease

The Janus kinase (JAK) enzyme family consists of 4 enzymes—tyrosine kinase 2 (TYK2), JAK1, JAK2, and JAK3—that function as intracellular transduction signals that mediate the biologic response of most extracellular cytokines and growth factors.[75] Critical psoriasis-related cytokines are dependent on intact JAK-STAT signaling, including IL-23, IL-12, and type I IFNs. In 2010, a genome-wide association identified *TYK2* as a psoriasis susceptibility locus,[76] and loss-of-function *TYK2* mutations confer a reduced risk for psoriasis.[77] Unlike other JAK isoforms, *TYK2* mediates biologic functions that are highly restricted to the immune responses associated with IL-23, IL-12, and type I IFN signaling.[78,79] For these reasons, blockade of *TYK2* signaling is an attractive therapeutic target for the potential treatment of psoriatic disease.

In September 2022, the FDA approved deucravacitinib as a first-in-class, oral, selective TYK2 inhibitor for the treatment of adult patients with moderate to severe plaque psoriasis. It was the first FDA approval of an oral small-molecule treatment for plaque psoriasis in nearly a decade. Deucravacitinib inhibits TYK2 signaling via selective binding of its unique regulatory domain, resulting in a conformational (allosteric) change that interferes with its active domain.[80] This novel mechanism of action limits the unwanted blockade of other broad biologic processes mediated by JAK1/2/3. Of note, the FDA did not issue any boxed warnings for deucravacitinib as it did for other FDA-approved JAK inhibitors.

In a head-to-head, 52-week, double-blind, prospective, randomized, phase 3 study, deucravacitinib showed clear superiority over apremilast for PASI75 at week 16 (53.0% [271/511] vs 39.8% [101/254]) and week 24 (58.7% [296/504] vs 37.8% [96/254]).[81] Clinical responses were sustained through week 52 and showed efficacy for difficult-to-treat areas such as the scalp, acral sites, and nails. Other advantages of deucravacitinib include once-daily dosing with no need for dose titration or adjustments for renal insufficiency as well as the absence of statistically significant differences in gastrointestinal tract symptoms compared to placebo. The most common adverse effects included nasopharyngitis, upper respiratory tract infections, headache, diarrhea, and herpes infections.[81] The potential benefit of deucravacitinib for PsA and psoriasis comorbidities remains to be seen, but it is promising due to its simultaneous disruption of multiple psoriasis-related cytokine networks. Several other TYK2 inhibitors are being developed for psoriatic disease and related inflammatory conditions, underscoring the promise of targeting this intracellular pathway.

Aryl Hydrocarbon Receptor Agonism

Topical steroids are the mainstay treatment option for localized or limited plaque psoriasis due to their potent immunosuppressive effect on the skin and relatively low cost. Combined with vitamin D analogs, topical steroids

result in marked improvements in disease severity and improved tolerability.[82] However, chronic use of topical steroids is limited by the need for twice-daily application, resulting in poor treatment compliance; loss of efficacy over time; risk for steroid-induced skin atrophy on special body sites; and patient concerns of potential systemic effects. The discovery of novel drug targets amenable to topical inhibition is needed.

Dysregulated aryl hydrocarbon receptor (AHR) levels have been reported in atopic dermatitis and psoriasis.[83] Aryl hydrocarbon receptors are ubiquitously expressed in many cell types and play an integral role in immune homeostasis within the skin, skin barrier function, protection against oxidative stressors, and regulation of proliferating melanocytes and keratinocytes.[84,85] They are widely expressed in multiple immune cell types (eg, antigen-presenting cells, T lymphocytes, fibroblasts) and modulate the differentiation of T17 and T22 cells as well as their balance with regulatory T-cell populations.[86] In keratinocytes, AHR helps to regulate terminal differentiation, enhance skin barrier integrity via AHR-dependent filaggrin (*FLG*) expression, and prevent transepidermal water loss.[87,88] The mechanisms by which AHR ligands lead to the upregulation or downregulation of specific genes is intricate and highly context dependent, such as the specific ligand and cell type involved. In preclinical studies, AHR-deficient mice develop psoriasiform skin inflammation, increased IL-17 and IL-22 expression, and abnormal skin barrier function.[89] Keratinocytes treated with AHR ligands in vitro modulated psoriasis-associated inflammatory cytokines, such as IL-6, IL-8, and type I and II IFNs.[89,90] The use of coal tar, one of the earliest historical treatments for psoriasis, is thought to activate AHRs in the skin via organic compound mixtures containing polyaromatic hydrocarbons that help normalize the proinflammatory environment in psoriatic skin.[91]

In June 2022, the FDA approved tapinarof as a first-in-class, topical, nonsteroidal AHR agonist for the treatment of plaque psoriasis in adults. Although the exact mechanism of action for tapinarof has not been fully elucidated, early studies suggest that its primary function is the activation of AHR, leading to reduced T-cell expansion and T17 cell differentiation. In the imiquimod mouse model, cytokine expression of IL-17A, IL-17F, IL-19, IL-22, IL-23A, and IL-lβ in psoriasiform skin lesions were downregulated following tapinarof treatment.[92] In humans, tapinarof treatment is associated with a remittive effect, in which the average time for tapinarof-treated psoriasis lesions to remain clear was approximately 4 months.[93] Preliminary research investigating the mechanism by which tapinarof induces this remittive effect is ongoing and may involve the reduced activation and influx of T17 and Trm populations into the skin.[94] However, these preclinical studies were performed on healthy dermatome-derived skin tissue cultured in T17-skewing conditions and needs to be replicated in larger samples sizes using human-derived psoriatic tissue. Alternatively, a strong inhibitory effect on IL-23 cytokine signaling may, in part, explain the remittive effect of tapinarof, as an analogous response is observed in patients who start and discontinue treatment with selective IL-23 antagonists. Regardless, the once-daily dosing of tapinarof and sustained treatment response is appealing to psoriasis patients. Tapinarof generally is well tolerated with mild folliculitis (>20% of patients) and contact dermatitis (5% of patients) reported as the most common skin-related adverse events.

New Roles for Phosphodiesterase 4 Inhibition

Phosphodiesterases (PDEs) are enzymes that hydrolyze cyclic nucleotides (eg, cyclic adenosine monophosphate) to regulate intracellular secondary messengers involved in the inflammatory response. One of several enzymes in the PDE family, PDE4, has been shown to have greater activity in psoriatic skin compared to healthy skin.[95] Phosphodiesterase inhibitors decrease the degradation of cyclic adenosine monophosphate, which triggers protein kinase A to downregulate proinflammatory (eg, TNF-α, IL-6, IL-17, IL-12, IL-23) cytokines and increased expression of anti-inflammatory signals such as IL-10.[96,97] Apremilast, the first oral PDE4 inhibitor approved by the FDA for psoriasis, offered a safe alternative to traditional oral immunosuppressive agents that had extensive risks and potential end-organ adverse effects. Unfortunately, apremilast demonstrated modest efficacy for psoriatic disease (better efficacy in the skin vs joint manifestations) and was supplanted easily by next-generation targeted biologic agents that were more efficacious and lacked the troublesome gastrointestinal tract adverse effects of PDE4 inhibition.[98]

Crisaborole became the first topical PDE4 inhibitor approved in the United States in December 2016 for twice-daily treatment of atopic dermatitis. Although phase 2 trial results were reported in psoriasis, this indication was never pursued, presumably due to similar improvements in primary outcome measures at week 12, compared to placebo (ClinicalTrials.gov Identifier NCT01300052).

In July 2022, the first topical PDE4 inhibitor indicated for plaque psoriasis was approved by the FDA—roflumilast cream 0.3% for once-daily use in individuals 12 years and older. Roflumilast was found to be clinically efficacious as early as 2 weeks after its use in an early-phase clinical trial.[99] In 2 phase 3 clinical trials (DERMIS-1 and DERMIS-2), roflumilast significantly increased the proportion of patients achieving PASI75 at week 8 compared to vehicle (39%–41.6% vs 5.3%–7.6%, respectively)($P<.001$).[100] Overall, this nonsteroidal topical therapy was found to be well tolerated, with infrequent reports of application site pain or irritation as adverse events. Similar to tapinarof, patients can apply roflumilast on all body surface areas including the face, external genitalia, and other intertriginous areas.[100] Importantly, the

broad immune impact of PDE4 inhibition suggests that topical roflumilast likely will be an effective treatment for several additional inflammatory conditions, including seborrheic dermatitis and atopic dermatitis, which would expand the clinical utility of this specific medication.

Conclusion

In the last 2 decades, we have witnessed a translational revolution in our understanding of the underlying genetics and immunology of psoriatic disease. Psoriasis is widely considered one of the best-managed inflammatory conditions in all of medicine due to the development and availability of highly targeted, effective topical and systemic therapies that predominantly disrupt IL-23/IL-17 cytokine signaling in affected tissues. However, future clinical studies and laboratory research are necessary to elucidate the precise cause of psoriasis as well as the underlying genetic and immune signaling pathways driving less common clinical variants and recalcitrant disease.

REFERENCES

1. Armstrong AW, Mehta MD, Schupp CW, et al. Psoriasis prevalence in adults in the United States. *JAMA Dermatol*. 2021;157:940-946. doi:10.1001/jamadermatol.2021.2007
2. Ogdie A, Langan S, Love T, et al. Prevalence and treatment patterns of psoriatic arthritis in the UK. *Rheumatology (Oxford)*. 2013;52:568-575. doi:10.1093/rheumatology/kes324
3. Mease PJ, Gladman DD, Papp KA, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. *J Am Acad Dermatol*. 2013;69:729-735. doi:10.1016/j.jaad.2013.07.023
4. Langan SM, Seminara NM, Shin DB, et al. Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. *J Invest Dermatol*. 2012;132(3 pt 1):556-562. doi:10.1038/jid.2011.365
5. Wu S, Li WQ, Han J, et al. Hypercholesterolemia and risk of incident psoriasis and psoriatic arthritis in US women. *Arthritis Rheumatol*. 2014;66:304-310. doi:10.1002/art.38227
6. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and hypertension: a systematic review and meta-analysis of observational studies. *J Hypertens*. 2013;31:433-442; discussion 442-443. doi:10.1097/HJH.0b013e32835bcce1
7. Gelfand JM, Dommasch ED, Shin DB, et al. The risk of stroke in patients with psoriasis. *J Invest Dermatol*. 2009;129:2411-2418. doi:10.1038/jid.2009.112
8. Armstrong AW, Lin SW, Chambers CJ, et al. Psoriasis and hypertension severity: results from a case-control study. *PLoS One*. 2011;6:E18227. doi:10.1371/journal.pone.0018227
9. Naldi L, Chatenoud L, Linder D, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. *J Invest Dermatol*. 2005;125:61-67. doi:10.1111/j.0022-202X.2005.23681.x
10. Yang YW, Kang JH, Lin HC. Increased risk of psoriasis following obstructive sleep apnea: a longitudinal population-based study. *Sleep Med*. 2012;13:285-289. doi:10.1016/j.sleep.2011.07.018
11. Vaengebjerg S, Skov L, Egeberg A, et al. Prevalence, incidence, and risk of cancer in patients with psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *JAMA Dermatol*. 2020;156:421-429. doi:10.1001/jamadermatol.2020.0024
12. Loft N, Skov L, Richardson C, et al. A nationwide population-based cohort study of the incidence of severe and rare infections among adults with psoriasis in Denmark. *Br J Dermatol*. 2022;187:353-363. doi:10.1111/bjd.21595
13. Fu Y, Lee CH, Chi CC. Association of psoriasis with inflammatory bowel disease: a systematic review and meta-analysis. *JAMA Dermatol*. 2018;154:1417-1423. doi:10.1001/jamadermatol.2018.3631
14. Dowlatshahi EA, Wakkee M, Arends LR, et al. The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: a systematic review and meta-analysis. *J Invest Dermatol*. 2014;134:1542-1551. doi:10.1038/jid.2013.508
15. Kurd SK, Troxel AB, Crits-Christoph P, et al. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. *Arch Dermatol*. 2010;146:891-895. doi:10.1001/archdermatol.2010.186
16. Elmets CA, Leonardi CL, Davis DMR, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. *J Am Acad Dermatol*. 2019;80:1073-1113. doi:10.1016/j.jaad.2018.11.058
17. Vanderpuye-Orgle J, Zhao Y, Lu J, et al. Evaluating the economic burden of psoriasis in the United States. *J Am Acad Dermatol*. 2015;72:961-967. doi:10.1016/j.jaad.2015.02.1099
18. Bos JD, Hagenaars C, Das PK, et al. Predominance of "memory" T cells (CD4+, CDw29+) over "naive" T cells (CD4+, CD45R+) in both normal and diseased human skin. *Arch Dermatol Res*. 1989;281:24-30. doi:10.1007/BF00424268
19. Bos JD, Hulsebosch HJ, Krieg SR, et al. Immunocompetent cells in psoriasis. in situ immunophenotyping by monoclonal antibodies. *Arch Dermatol Res*. 1983;275:181-189. doi:10.1007/BF00510050
20. Griffiths CE, Powles AV, Leonard JN, et al. Clearance of psoriasis with low dose cyclosporin. *Br Med J (Clin Res Ed)*. 1986;293:731-732. doi:10.1136/bmj.293.6549.731
21. Ellis CN, Gorsulowsky DC, Hamilton TA, et al. Cyclosporine improves psoriasis in a double-blind study. *JAMA*. 1986;256:3110-3116.
22. Langrish CL, Chen Y, Blumenschein WM, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J Exp Med*. 2005;201:233-240. doi:10.1084/jem.20041257
23. Ferber IA, Brocke S, Taylor-Edwards C, et al. Mice with a disrupted IFN-gamma gene are susceptible to the induction of experimental autoimmune encephalomyelitis (EAE). *J Immunol*. 1996;156:5-7.
24. Bharadwaj R, Lusi CF, Mashayekh S, et al. Methotrexate suppresses psoriatic skin inflammation by inhibiting muropeptide transporter SLC46A2 activity. *Immunity*. 2023;56:998-1012. doi:10.1016/j.immuni.2023.04.001
25. Jenneck C, Novak N. The safety and efficacy of alefacept in the treatment of chronic plaque psoriasis. *Ther Clin Risk Manag*. 2007;3:411-420.
26. Pariser DM, Gordon KB, Papp KA, et al. Clinical efficacy of efalizumab in patients with chronic plaque psoriasis: results from three randomized placebo-controlled phase III trials: part I. *J Cutan Med Surg*. 2005;9:303-312. doi:10.1007/s10227-005-0116-1
27. Mease PJ, Gottlieb AB, van der Heijde D, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. *Ann Rheum Dis*. 2017;76:1550-1558. doi:10.1136/annrheumdis-2016-210724
28. Hawkes JE, Yan BY, Chan TC, et al. Discovery of the IL-23/IL-17 signaling pathway and the treatment of psoriasis. *J Immunol*. 2018;201:1605-1613. doi:10.4049/jimmunol.1800013
29. Ogawa K, Okada Y. The current landscape of psoriasis genetics in 2020. *J Dermatol Sci*. 2020;99:2-8. doi:10.1016/j.jdermsci.2020.05.008
30. Arakawa A, Siewert K, Stohr J, et al. Melanocyte antigen triggers autoimmunity in human psoriasis. *J Exp Med*. 2015;212:2203-2212. doi:10.1084/jem.20151093
31. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet*. 2007;370:263-271. doi:10.1016/S0140-6736(07)61128-3
32. Wang CQF, Akalu YT, Suarez-Farinas M, et al. IL-17 and TNF synergistically modulate cytokine expression while suppressing melanogenesis: potential relevance to psoriasis. *J Invest Dermatol*. 2013;133:2741-2752. doi:10.1038/jid.2013.237
33. Cheung KL, Jarrett R, Subramaniam S, et la. Psoriatic T cells recognize neolipid antigens generated by mast cell phospholipase delivered by exosomes and presented by CD1a. *J Exp Med*. 2016;213:2399-2412. doi:10.1084/jem.20160258

34. Hawkes JE, Gonzalez JA, Krueger JG. Autoimmunity in psoriasis: evidence for specific autoantigens. *Curr Dermatol Rep*. 2017;6:104-112. doi:10.1007/s13671-017-0177-6
35. Johansen C, Usher PA, Kjellerup RB, et al. Characterization of the interleukin-17 isoforms and receptors in lesional psoriatic skin. *Br J Dermatol*. 2009;160:319-324. doi:10.1111/j.1365-2133.2008.08902.x
36. Kolbinger F, Loesche C, Valentin MA, et al. beta-Defensin 2 is a responsive biomarker of IL-17A-driven skin pathology in patients with psoriasis. *J Allergy Clin Immunol*. 2017;139:923-932. doi:10.1016/j.jaci.2016.06.038
37. Ruddy MJ, Wong GC, Liu XK, et al. Functional cooperation between interleukin-17 and tumor necrosis factor-alpha is mediated by CCAAT/enhancer-binding protein family members. *J Biol Chem*. 2004;279:2559-2567. doi:10.1074/jbc.M308809200
38. Shen F, Hu Z, Goswami J, et al. Identification of common transcriptional regulatory elements in interleukin-17 target genes. *J Biol Chem*. 2006;281:24138-24148. doi:10.1074/jbc.M604597200
39. Harper EG, Guo C, Rizzo H, et al. Th17 cytokines stimulate CCL20 expression in keratinocytes in vitro and in vivo: implications for psoriasis pathogenesis. *J Invest Dermatol*. 2009;129:2175-2183. doi:10.1038/jid.2009.65
40. 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;131:677-687. doi:10.1038/jid.2010.340
41. Homey B, Dieu-Nosjean MC, Wiesenborn A, et al. Up-regulation of macrophage inflammatory protein-3 alpha/CCL20 and CC chemokine receptor 6 in psoriasis. *J Immunol*. 2000;164:6621-6632. doi:10.4049/jimmunol.164.12.6621
42. Stephen-Victor E, Fickenscher H, Bayry J. IL-26: an emerging proinflammatory member of the IL-10 Cytokine family with multifaceted actions in antiviral, antimicrobial, and autoimmune responses. *PLoS Pathog*. 2016;12:E1005624. doi:10.1371/journal.ppat.1005624
43. Wolk K, Witte K, Witte E, et al. IL-29 is produced by T(H)17 cells and mediates the cutaneous antiviral competence in psoriasis [published online September 25, 2013]. *Sci Transl Med*. doi:10.1126/scitranslmed.3006245
44. Kasprowicz-Furmanczyk M, Czerwinska J, Placek W, et al. Assessment of the tissue resident memory cells in lesional skin of patients with psoriasis and in healthy skin of healthy volunteers. *Int J Environ Res Public Health*. 2021;18:11251. doi:10.3390/ijerph182111251
45. Cheuk S, Schlums H, Gallais Serezal I, et al. CD49a expression defines tissue-resident CD8(+) T cells poised for cytotoxic function in human skin. *Immunity*. 2017;46:287-300. doi:10.1016/j.immuni.2017.01.009
46. Sawyer LM, Malottki K, Sabry-Grant C, et al. Assessing the relative efficacy of interleukin-17 and interleukin-23 targeted treatments for moderate-to-severe plaque psoriasis: a systematic review and network meta-analysis of PASI response. *PLoS One*. 2019;14:E0220868. doi:10.1371/journal.pone.0220868
47. Coates LC, Kavanaugh A, Mease PJ, et al. Group for research and assessment of psoriasis and psoriatic arthritis 2015 treatment recommendations for psoriatic arthritis. *Arthritis Rheumatol*. 2016;68:1060-1071. doi:10.1002/art.39573
48. Wang EA, Suzuki E, Maverakis E, et al. Targeting IL-17 in psoriatic arthritis. *Eur J Rheumatol*. 2017;4:272-277. doi:10.5152/eurjrheum.2017.17037
49. Armstrong A, Fahrbach K, Leonardi C, et al. Efficacy of bimekizumab and other biologics in moderate to severe plaque psoriasis: a systematic literature review and a network meta-analysis. *Dermatol Ther (Heidelb)*. 2022;12:1777-1792. doi:10.1007/s13555-022-00760-8
50. van Baarsen LG, Lebre MC, van der Coelen D, et al. Heterogeneous expression pattern of interleukin 17A (IL-17A), IL-17F and their receptors in synovium of rheumatoid arthritis, psoriatic arthritis and osteoarthritis: possible explanation for nonresponse to anti-IL-17 therapy? *Arthritis Res Ther*. 2014;16:426. doi:10.1186/s13075-014-0426-z
51. Hot A, Zrioual S, Toh ML, et al. IL-17A- versus IL-17F-induced intracellular signal transduction pathways and modulation by IL-17RA and IL-17RC RNA interference in rheumatoid synoviocytes. *Ann Rheum Dis*. 2011;70:341-348. doi:10.1136/ard.2010.132233
52. Adams R, Maroof A, Baker T, et al. Bimekizumab, a novel humanized IgG1 antibody that neutralizes both IL-17A and IL-17F. *Front Immunol*. 2020;11:1894. doi:10.3389/fimmu.2020.01894
53. Gordon KB, Foley P, Krueger JG, et al. Bimekizumab efficacy and safety in moderate to severe plaque psoriasis (BE READY): a multicentre, double-blind, placebo-controlled, randomised withdrawal phase 3 trial. *Lancet*. 2021;397:475-486. doi:10.1016/S0140-6736(21)00126-4
54. 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;77:523-532. doi:10.1136/annrheumdis-2017-212127
55. Gordon KB, Langley RG, Warren RB, et al. Bimekizumab safety in patients with moderate to severe plaque psoriasis: pooled results from phase 2 and phase 3 randomized clinical trials. *JAMA Dermatol*. 2022;158:735-744. doi:10.1001/jamadermatol.2022.1185
56. Reich K, Warren RB, Lebwohl M, et al. Bimekizumab versus secukinumab in plaque psoriasis. *N Engl J Med*. 2021;385:142-152. doi:10.1056/NEJMoa2102383
57. Reich K, Iversen L, Puig L, et al. Long-term efficacy and safety of brodalumab in moderate-to-severe plaque psoriasis: a post hoc pooled analysis of AMAGINE-2 and -3. *J Eur Acad Dermatol Venereol*. 2022;36:1275-1283. doi:10.1111/jdv.18068
58. Papp KA, Blauvelt A, Puig L, et al. Long-term safety and efficacy of risankizumab for the treatment of moderate-to-severe plaque psoriasis: interim analysis of the LIMMitless open-label extension trial up to 5 years of follow-up. *J Am Acad Dermatol*. 2023;89:1149-1158. doi: 10.1016/j.jaad.2023.07.1024
59. Glatt S, Jemec GBE, Forman S, et al. Efficacy and safety of bimekizumab in moderate to severe hidradenitis suppurativa: a phase 2, double-blind, placebo-controlled randomized clinical trial. *JAMA Dermatol*. 2021;157:1279-1288. doi:10.1001/jamadermatol.2021.2905
60. Choon SE, Lai NM, Mohammad NA, et al. Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia. *Int J Dermatol*. 2014;53:676-684. doi:10.1111/ijd.12070
61. Zheng M, Jullien D, Eyerich K. The prevalence and disease characteristics of generalized pustular psoriasis. *Am J Clin Dermatol*. 2022;23(suppl 1):5-12. doi:10.1007/s40257-021-00664-x
62. Fujita H, Gooderham M, Romiti R. Diagnosis of generalized pustular psoriasis. *Am J Clin Dermatol*. 2022;23(suppl 1):31-38. doi:10.1007/s40257-021-00652-1
63. Choon SE, Navarini AA, Pinter A. Clinical course and characteristics of generalized pustular psoriasis. *Am J Clin Dermatol*. 2022;23(suppl 1):21-29. doi:10.1007/s40257-021-00654-z
64. Augey F, Renaudier P, Nicolas JF. Generalized pustular psoriasis (Zumbusch): a French epidemiological survey. *Eur J Dermatol*. 2006;16:669-673.
65. Ohkawara A, Yasuda H, Kobayashi H, et al. Generalized pustular psoriasis in Japan: two distinct groups formed by differences in symptoms and genetic background. *Acta Derm Venereol*. 1996;76:68-71. doi:10.2340/00015555766871
66. Lee JY, Kang S, Park JS, et al. Prevalence of psoriasis in Korea: A population-based epidemiological study using the Korean National Health Insurance database. *Ann Dermatol*. 2017;29:761-767. doi:10.5021/ad.2017.29.6.761
67. Prinz JC, Choon SE, Griffiths CEM, et al. Prevalence, comorbidities and mortality of generalized pustular psoriasis: a literature review. *J Eur Acad Dermatol Venereol*. 2023;37:256-273. doi:10.1111/jdv.18720
68. Johnston A, Xing X, Wolterink L, et al. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. *J Allergy Clin Immunol*. 2017;140:109-120. doi:10.1016/j.jaci.2016.08.056
69. Rajan N, Sinclair N, Nakai H, et al. A tale of two sisters: identical *IL36RN* mutations and discordant phenotypes. *Br J Dermatol*. 2016;174:417-420. doi:10.1111/bjd.14003
70. Ly K, Beck KM, Smith MP, et al. Diagnosis and screening of patients with generalized pustular psoriasis. *Psoriasis (Auckl)*. 2019;9:37-42. doi:10.2147/PTT.S181808

71. Sugiura K. Role of interleukin 36 in generalised pustular psoriasis and beyond. *Dermatol Ther (Heidelb)*. 2022;12:315-328. doi:10.1007/s13555-021-00677-8
72. Akiyama M, Takeichi T, McGrath JA, et al. Autoinflammatory keratinization diseases: an emerging concept encompassing various inflammatory keratinization disorders of the skin. *J Dermatol Sci*. 2018;90:105-111. doi:10.1016/j.jdermsci.2018.01.012
73. Bachelez H, Choon SE, Marrakchi S, et al. Trial of spesolimab for generalized pustular psoriasis. *N Engl J Med*. 2021;385:2431-2440. doi:10.1056/NEJMoa2111563
74. Warren RB, Reich A, Kaszuba A, et al. Imsidolimab, an anti-IL-36 receptor monoclonal antibody for the treatment of generalised pustular psoriasis: results from the phase 2 GALLOP trial. *Br J Dermatol*. 2023;189:161-169. doi:10.1093/bjd/ljad083
75. Villarino AV, Kanno Y, O'Shea JJ. Mechanisms and consequences of Jak-STAT signaling in the immune system. *Nat Immunol*. 2017;18:374-384. doi:10.1038/ni.3691
76. Genetic Analysis of Psoriasis Consortium & the Wellcome Trust Case Control Consortium 2; Strange A, Capon F, et al. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. *Nat Genet*. 2010;42:985-990. doi:10.1038/ng.694
77. Enerback C, Sandin C, Lambert S, et al. The psoriasis-protective TYK2 I684S variant impairs IL-12 stimulated pSTAT4 response in skin-homing CD4+ and CD8+ memory T-cells. *Sci Rep*. 2018;8:7043. doi:10.1038/s41598-018-25282-2
78. Shimoda K, Kato K, Aoki K, et al. Tyk2 plays a restricted role in IFN alpha signaling, although it is required for IL-12-mediated T cell function. *Immunity*. 2000;13:561-571. doi:10.1016/s1074-7613(00)00055-8
79. Karaghiosoff M, Neubauer H, Lassnig C, et al. Partial impairment of cytokine responses in Tyk2-deficient mice. *Immunity*. 2000;13:549-560. doi:10.1016/s1074-7613(00)00054-6
80. Burke JR, Cheng L, Gillooly KM, et al. Autoimmune pathways in mice and humans are blocked by pharmacological stabilization of the TYK2 pseudokinase domain [published online July 24, 2019]. *Sci Transl Med*. doi:10.1126/scitranslmed.aaw1736
81. Strober B, Thaci D, Sofen H, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, phase 3 program for evaluation of TYK2 inhibitor psoriasis second trial. *J Am Acad Dermatol*. 2023;88:40-51. doi:10.1016/j.jaad.2022.08.061
82. Stein Gold L, Lebwohl M, Menter A, et al. Aerosol foam formulation of fixed combination calcipotriene plus betamethasone dipropionate is highly efficacious in patients with psoriasis vulgaris: pooled data from three randomized controlled studies. *J Drugs Dermatol*. 2016;15:951-957.
83. Beranek M, Fiala Z, Kremlacek J, et al. Serum levels of aryl hydrocarbon receptor, cytochromes p450 1a1 and 1b1 in patients with exacerbated psoriasis vulgaris. *Folia Biol (Praha)*. 2018;64:97-102.
84. Esser C, Rannug A. The aryl hydrocarbon receptor in barrier organ physiology, immunology, and toxicology. *Pharmacol Rev*. 2015;67:259-279. doi:10.1124/pr.114.009001
85. Furue M, Uchi H, Mitoma C, et al. Antioxidants for healthy skin: the emerging role of aryl hydrocarbon receptors and nuclear factor-erythroid 2-related factor-2. *Nutrients*. 2017;9:223. doi:10.3390/nu9030223
86. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*. 2008;371:1675-1684. doi:10.1016/S0140-6736(08)60726-6
87. Sutter CH, Olesen KM, Bhuju J, et al. AHR regulates metabolic reprogramming to promote SIRT1-dependent keratinocyte differentiation. *J Invest Dermatol*. 2019;139:818-826. doi:10.1016/j.jid.2018.10.019
88. Haas K, Weighardt H, Deenen R, et al. Aryl hydrocarbon receptor in keratinocytes is essential for murine skin barrier integrity. *J Invest Dermatol*. 2016;136:2260-2269. doi:10.1016/j.jid.2016.06.627
89. Di Meglio P, Duarte JH, Ahlfors H, et al. Activation of the aryl hydrocarbon receptor dampens the severity of inflammatory skin conditions. *Immunity*. 2014;40:989-1001. doi:10.1016/j.immuni.2014.04.019
90. Kim HO, Kim JH, Chung BY, et al. Increased expression of the aryl hydrocarbon receptor in patients with chronic inflammatory skin diseases. *Exp Dermatol*. 2014;23:278-281. doi:10.1111/exd.12350
91. van den Bogaard EH, Bergboer JG, Vonk-Bergers M, et al. Coal tar induces AHR-dependent skin barrier repair in atopic dermatitis. *J Clin Invest*. 2013;123:917-927. doi:10.1172/JCI65642
92. Smith SH, Jayawickreme C, Rickard DJ, et al. Tapinarof is a natural AHR agonist that resolves skin inflammation in mice and humans. *J Invest Dermatol*. 2017;137:2110-2119. doi:10.1016/j.jid.2017.05.004
93. Strober B, Stein Gold L, Bissonnette R, et al. One-year safety and efficacy of tapinarof cream for the treatment of plaque psoriasis: results from the PSOARING 3 trial. *J Am Acad Dermatol*. 2022;87:800-806. doi:10.1016/j.jaad.2022.06.1171
94. Mooney N, Teague JE, Gehad AE, et al. Tapinarof inhibits the formation, cytokine production, and persistence of resident memory T cells in vitro. *SKIN J Cutan Med*. 2023;7:S194. doi:10.25251/skin.7.supp.194
95. Schafer PH, Truzzi F, Parton A, et al. Phosphodiesterase 4 in inflammatory diseases: effects of apremilast in psoriatic blood and in dermal myofibroblasts through the PDE4/CD271 complex. *Cell Signal*. 2016;28:753-763. doi:10.1016/j.cellsig.2016.01.007
96. Li H, Zuo J, Tang W. Phosphodiesterase-4 inhibitors for the treatment of inflammatory diseases. *Front Pharmacol*. 2018;9:1048. doi:10.3389/fphar.2018.01048
97. Schafer PH, Parton A, Gandhi AK, et al. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. *Br J Pharmacol*. 2010;159:842-855. doi:10.1111/j.1476-5381.2009.00559.x
98. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *J Am Acad Dermatol*. 2015;73:37-49. doi:10.1016/j.jaad.2015.03.049
99. Papp KA, Gooderham M, Droege M, et al. Roflumilast cream improves signs and symptoms of plaque psoriasis: results from a phase 1/2a randomized, controlled study. *J Drugs Dermatol*. 2020;19:734-740. doi:10.36849/JDD.2020.5370
100. Lebwohl MG, Kircik LH, Moore AY, et al. Effect of roflumilast cream vs vehicle cream on chronic plaque psoriasis: the DERMIS-1 and DERMIS-2 randomized clinical trials. *JAMA*. 2022;328:1073-1084. doi:10.1001/jama.2022.15632

APPENDIX

Novel Biologic and Topical Therapies for the Treatment of PsO and PsA

Drug class	Drug name	Biologic target	Psoriasis indication(s)	Administration (maintenance dose)	Approved patient population
TNF inhibitor	Certolizumab pegol	TNF	PsO, PsA	SubQ (200 mg once every 2 wk)	Adults
	Adalimumab	TNF	PsO, PsA	SubQ (40 mg once every 2 wk)	Adults
	Etanercept	TNF	PsO, PsA	SubQ (50 mg once weekly)	Adults
	Infliximab	TNF	PsO, PsA	IV infusion (5–10 mg/kg once every 8 wk)	Adults, children ≥4 y (PsO only)
IL-17 inhibitor	Secukinumab	IL-17A	PsO, PsA	SubQ (300 mg once every 4 wk)	Adults, children ≥6 y (PsO only) and ≥2 y (PsA only)
	Ixekizumab	IL-17A	PsO, PsA	SubQ (80 mg once every 4 wk)	Adults, children ≥6 y (PsO only)
	Brodalumab	IL-17R	PsO	SubQ (210 mg once every 2 wk)	Adults
	Bimekizumab	IL-17A/F	PsO	SubQ (320 mg once every 4–8 wk)	Adults
IL-23 inhibitor	Ustekinumab	IL-12/23p40	PsO, PsA	Adults: subQ (45 or 90 mg once every 12 wk); children ≥6 y: subQ (<60 kg: 0.75 mg/kg; 60–100 kg: 45 mg; >100 kg: 90 mg)	Adults, children ≥6 y
	Tildrakizumab	IL-23p19	PsO	SubQ (100 mg once every 12 wk)	Adults
	Guselkumab	IL-23p19	PsO, PsA	SubQ (100 mg once every 8 wk)	Adults
	Risankizumab	IL-23p19	PsO, PsA	SubQ (150 mg once every 12 wk)	Adults
AHR agonist	Tapinarof	AHR	PsO	Topical (once daily)	Adults
PDE4 inhibitor	Roflumilast	PDE4	PsO	Topical (once daily)	Adults, children ≥12 y
	Apremilast	PDE4	PsO, PsA	Oral (30 mg twice daily)	Adults
JAK inhibitor	Deucravacitinib	TYK2	PsO	Oral (6 mg once daily)	Adults
IL-36 inhibitor	Spesolimab	IL-36R	GPP	IV (one 900-mg injection, repeat in 7 d if needed)	Adults

Abbreviations: AHR, aryl hydrocarbon receptor; GPP, generalized pustular psoriasis; IL-17R, IL-17 receptor; IL-36R, IL-36 receptor; IV, intravenous; JAK, Janus kinase; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis; PsO, plaque psoriasis; subQ, subcutaneous; TNF, tumor necrosis factor; TYK2, tyrosine kinase.