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REVIEW

Psoriasis: Unraveling Disease Mechanisms and Advancing Pharmacological and Nanotechnological Treatments

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Abstract: Research into the pathogenesis of inflammatory skin diseases, including dermatitis and psoriasis, has yielded significant advancements in the last decades. The identification of age, gender, and genetic factors contributing to these complex conditions has been pivotal in developing novel pharmacological and technological treatments. This review delves into the molecular underpinnings of psoriasis, examining current therapies and promising investigational agents. We highlight the potential of nanotechnology to enhance drug delivery to affected skin areas, with microneedles emerging as a promising platform for psoriasis and other chronic inflammatory skin diseases.

Keywords: biodegradable nanoparticles, clinical trials, skin inflammatory diseases, psoriasis, microneedles

Introduction

Psoriasis is a chronic inflammatory skin disease primarily influenced by genetics and aging, though environmental factors like trauma (Koebner phenomenon), infections, and certain medications can also contribute. With a global prevalence of approximately 2%, psoriasis exhibits variations across populations, with higher rates observed in Caucasians and Scandinavians (up to 11%).[1,2] The condition manifests in several forms, with plaque psoriasis being the most common (90%), characterized by itchy, scaly patches.[3] Both innate and adaptive immune responses underlie psoriatic inflammation, although the innate response is more prominent in plaque psoriasis.[4]

One proposed mechanism for psoriasis involves the overexpression of antimicrobial peptides, such as LL-37, β-defensins, and S100 proteins, which trigger and sustain inflammation.[5,6] Initially, a decline in LL-37 and other antimicrobial peptides occurs in keratinocytes following stress, like physical injury. Released LL-37 forms complexes with cellular DNA, stimulating toll-like receptor 9 on plasmacytoid dendritic cells, contributing to psoriasis pathogenesis.[7] LL-37 induces type I interferon production, promoting dendritic cell maturation and driving Th1 and Th17 differentiation.[6–8] Th17 cells, characterized by IL-17, IL-22, IL-21, TNF-α production and RORC expression, play a crucial role in psoriasis.[9,10] Elevated RORC mRNA in psoriatic patients supports the involvement of Th17 cells in disease pathogenesis.[11] RORγt, a key Th17 transcription factor, is encoded by the Rorg gene along with its isoform ROR. While sharing the same C-terminal region, they differ in their N-terminals.[12] Beyond Th17 cells, RORγt influences cytokine production in CD8+Tc17 cells, invariant natural killer T cells, ILC3s, and γδ T cells, contributing to autoimmune inflammation.[13] RORγ-deficient mice exhibit reduced Th17/IL-17 responses and protection from psoriasis-like inflammation.[14] Targeting RORγt with small molecule inhibitors offers a potential therapeutic strategy to suppress the proinflammatory IL-17/IL-23 axis. As a nuclear hormone receptor, RORγt's activity is ligand-dependent, making its

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ligand binding domain an attractive target for drug development. Several inhibitors have shown efficacy in preclinical models.[15–19] Figure 1 illustrates the core hypothesis underlying plaque-type psoriasis pathogenesis.

The IL-17 receptor complex, upon interacting with ACT1, activates several intracellular kinases including ERK, p38 MAPK, TAK1, IKK, and GSK-3β. These kinases subsequently stimulate the production of proinflammatory cytokines, chemokines, and antimicrobial peptides. While Th1 and Th2 cytokine signaling is mediated by JAK-STAT pathways, Th17 responses involve ACT1 and NF-κB.[20,21] Notably, γδ T cells can produce IL-17A independently of IL-23 stimulation.[22] Pustular psoriasis, characterized by coalescing sterile pustules, differs markedly from plaque psoriasis. While adaptive immunity is central to plaque psoriasis pathogenesis, and therapies targeting these mechanisms are effective, pustular psoriasis primarily involves the innate immune system and responds less favorably to plaque psoriasis treatments.[8,23–25] Although sharing some metabolic pathways, these psoriasis types exhibit distinct pathogenic mechanisms. Pustular psoriasis predominantly relies on keratinocytes, neutrophils, and monocytes.[26] A mutation in the IL36RN gene leads to increased IL-1β, IL-36α, and IL-36γ expression, driving neutrophil accumulation in the epidermis.[26–28] The elevated levels of neutrophil chemokines CXCL1, CXCL2, and CXCL8 (IL-8) support this pathogenic model.[26]

Generalized pustular psoriasis is an acute, rapidly progressing condition characterized by widespread redness and pus-filled blisters, often accompanied by systemic symptoms.[27–29] In contrast, guttate psoriasis primarily affects children and

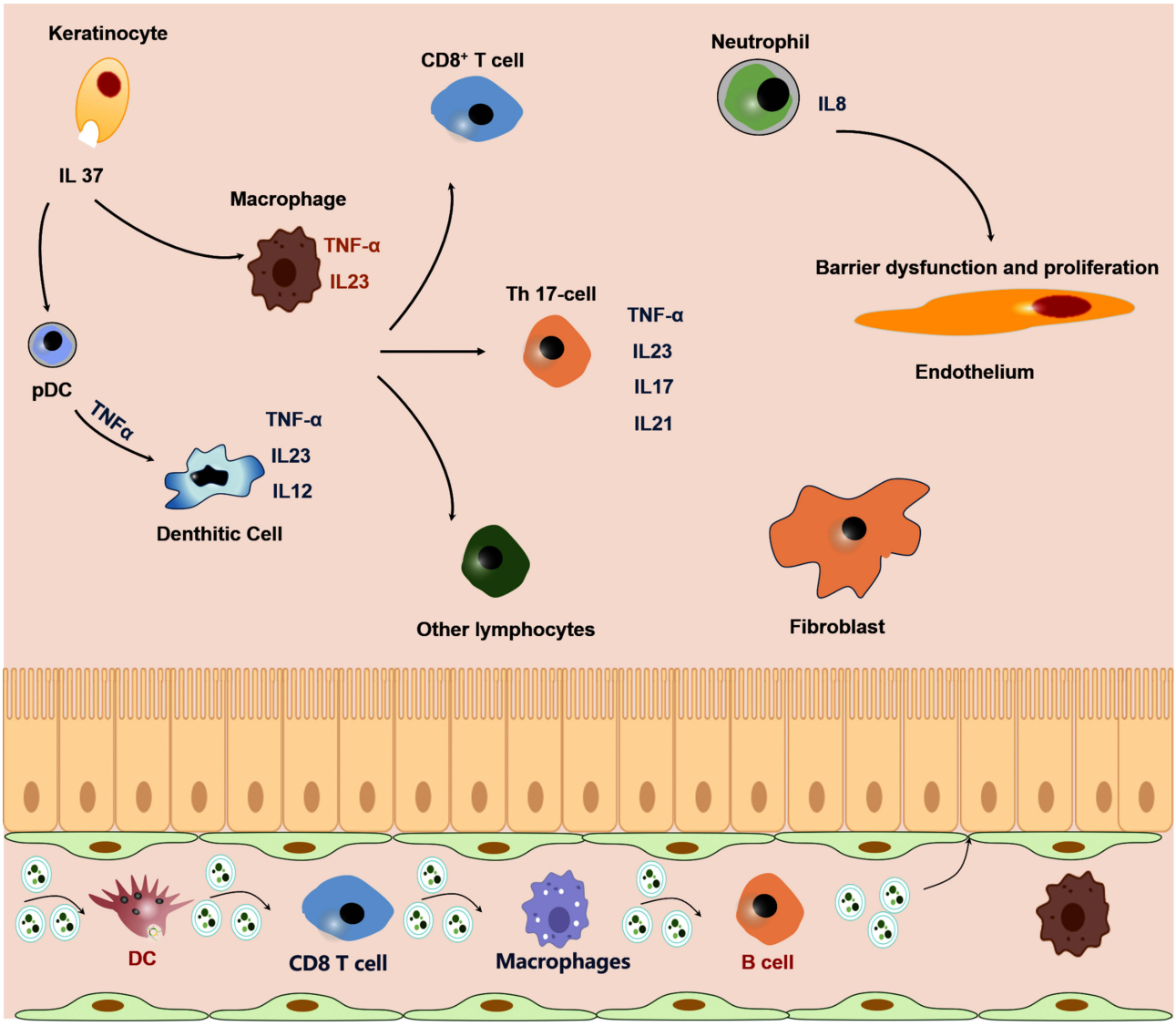

Figure 1 Plaque-type psoriasis pathogenesis principal hypothesis.

adolescents, manifesting as small, red scaly patches. While its pathophysiology likely mirrors that of plaque psoriasis, a potential link to streptococcal superantigens has been suggested, involving molecular mimicry in HLA-Cw6 positive individuals.[18,30–32] Inverse psoriasis, affecting skin folds, presents with erosive rather than scaly lesions. Although its underlying mechanisms remain similar to plaque psoriasis, a decreased number of CD161+ cells in affected areas, potentially due to microbial colonization, has been observed.[33,34] Erythrodermic psoriasis, the most severe form, involves widespread inflammation and skin redness, without apparent deviations from the typical psoriasis pathophysiology. This review explores the molecular foundations of psoriasis, evaluating current treatments and promising new investigational therapies. We emphasize the role of nanotechnology in improving drug delivery to affected skin areas, highlighting microneedles as an emerging and promising platform for treating psoriasis and other chronic inflammatory skin conditions.

Clinical Presentation

Chronic Plaque

Psoriasis vulgaris, the most common form of chronic plaque psoriasis, is characterized by well-defined, salmon-pink plaques with silvery scales on white skin (Figure 2A) or gray plaques on black skin (Figure 2B), the condition often exhibits the Auspitz sign: pinpoint bleeding upon scale removal. Plaques vary widely in size and thickness, with smaller plaques indicating active disease and thinner plaques often responding better to phototherapy.[35,36] Individual plaques expand outward, creating a central clearing with an annular appearance. Commonly affecting the knees, elbows, lumbosacral region, and scalp, psoriasis can involve any skin surface. Symmetrical plaque distribution is characteristic (Figure 2C). In severe cases, trauma or pressure can induce new lesions (Koebner phenomenon).[37,38]

Other Subtypes of Psoriasis

Guttate psoriasis, comprising 2% of cases (Figure 2D), is characterized by numerous, small and scaly papules. Often preceded by pharyngitis or tonsillitis, with elevated antistreptolysin O, anti-DNase B, or streptozyme titers in approximately half of patients, guttate psoriasis typically resolves spontaneously within weeks or months in children and young adults.[39,40] However, approximately 40% progress to chronic plaque psoriasis. The role of antibiotics in management is unclear, while tonsillectomy may be beneficial for recurrent cases associated with tonsillitis. Factors determining disease resolution or persistence remain unknown.[41,42]

Erythroderma, a severe psoriasis condition characterized by widespread erythema and scaling, can lead to a range of complications including hypothermia, high-output cardiac failure, electrolyte imbalances, and intense itching and pain (Figure 2E).[43,44] Pustular psoriasis, a group of rare psoriasis variants with distinct morphologies, includes generalized pustular psoriasis (von Zumbusch disease), palmoplantar pustulosis, and acrodermatitis continua of Hallopeau. Generalized pustular psoriasis (Figure 2F) is a potentially life-threatening autoimmune condition characterized by recurrent flares, sterile pustules, and fever.[45,46] Unlike chronic plaque psoriasis, it affects women more frequently and can be triggered by corticosteroid withdrawal, hypocalcemia, pregnancy, or infection. Palmoplantar pustulosis (Figure 2G) primarily affects middle-aged female smokers, manifesting as sterile yellow pustules on palms and soles that resolve to red or brown macules.[47,48] Approximately 20% of cases coexist with chronic plaque psoriasis. Acrodermatitis continua of Hallopeau, a rare condition, involves pustules on fingers and toes, sometimes leading to nail loss. Approximately 40% of individuals with this condition also have chronic plaque psoriasis.[49,50]

Psoriasis can also manifest in location-specific variants, such as inverse (flexural), palmoplantar, sebopsoriasis, and nail psoriasis, in addition to the more common guttate, erythrodermic, and pustular forms.[51,52] Inverse psoriasis affects skin folds, presenting as shiny, red, non-scaling lesions (Figure 2H), often mimicking candidiasis or fungal infections.[53,54] Sebopsoriasis affects the scalp, face, and upper chest, with its relationship to seborrheic dermatitis and dandruff remaining debated. Nail psoriasis, affecting approximately 50% of plaque psoriasis patients, presents with diverse manifestations, including pitting, onycholysis (Figure 2I), oil spots, and nail dystrophy.[55,56] Onycholysis specifically doubles the risk of psoriatic arthritis and correlates with longer disease duration compared to psoriasis without nail involvement (Figure 2J).

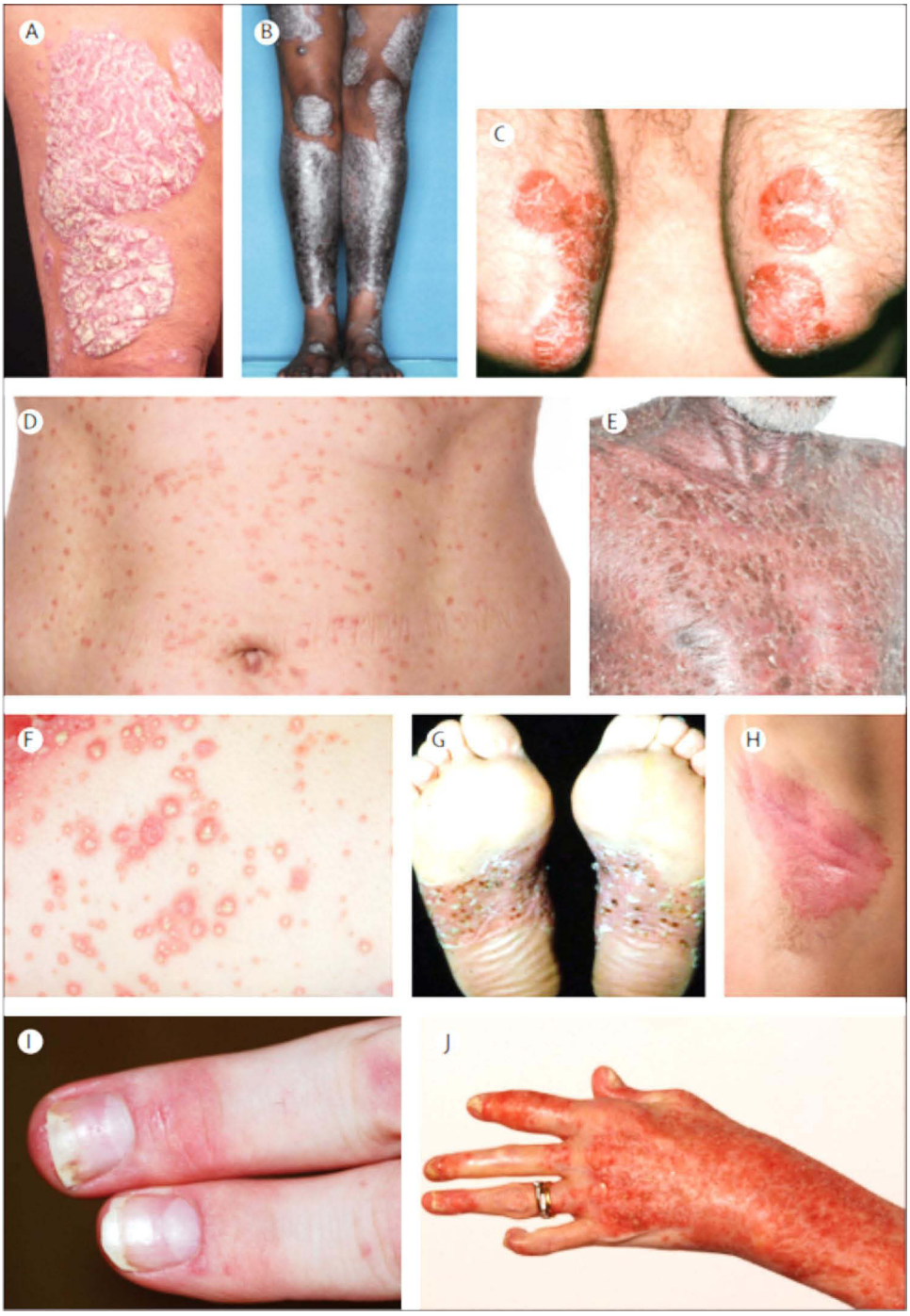

Figure 2 Various clinical presentations of psoriasis and its subtypes. (**A**) A well demarcated, pink plaque on white skin. (**B**) On black skin, the plaques are grey. (**C**) Symmetry of plaques is characteristic. (**D**) Small centripetal papules in guttate psoriasis. (**E**) Erythroderma. (**F**) Generalised pustular psoriasis. (**G**) Palmoplantar pustulosis. (**H**) Flexural or inverse psoriasis with absence of scale. (**I**) Nail pitting and onycholysis. (**J**) Psoriatic arthritis with dactylitis and nail changes.

Pathophysiology

Histological Features

Psoriatic histology demonstrates epidermal thickening (acanthosis) with elongated rete ridges, a reduced or absent granular layer, dilated capillaries, and suprapapillary thinning.[57,58] The dermis and epidermis exhibit a T cell-predominant inflammatory infiltrate, often accompanied by neutrophil clusters within parakeratotic scales (Munro

microabscesses). In pustular psoriasis, neutrophil clusters within pustules (Kogoj spongiform micropustules) serve as a diagnostic hallmark.[59,60]

Pathogenesis

Recent immunological and genetic research has illuminated critical immune pathways involved in psoriasis pathogenesis, particularly the roles of IL-17, IL-23, and TNFα. Psoriasis is characterized by a dysregulated immune response, where the interplay between the innate and adaptive immune systems results in chronic inflammation and epidermal hyperplasia.[61] Central to this process is the interaction between keratinocytes and immune cells, such as T helper (Th) 17 cells.

The IL-23/Th17 axis has emerged as a key pathogenic pathway. IL-23, produced by antigen-presenting cells like dendritic cells, activates Th17 cells that subsequently secrete IL-17. This cytokine not only promotes keratinocyte proliferation and activation but also amplifies the inflammatory response by inducing the release of other pro-inflammatory cytokines, such as IL-6 and TNFα. The feedforward loop created by IL-17 induces a vicious cycle of continuous inflammation, which leads to the hallmark symptoms of psoriasis, including thickened, scaly plaques.[62] TNFα, a potent pro-inflammatory cytokine, plays a critical role in the pathogenesis of psoriasis by enhancing the activation of both innate and adaptive immune responses. TNFα contributes to the development and maintenance of the disease through its effects on keratinocytes, endothelial cells, and immune cells. It further facilitates the dysregulation of the immune system, exacerbating inflammation and leading to the development of psoriasis lesions. Clinical evidence has shown that TNFα inhibitors significantly reduce disease activity, underscoring its pivotal role in the disease process.[63] The genetic component of psoriasis also plays a crucial role, with several susceptibility loci identified through genome-wide association studies (GWAS). These loci, which include genes related to immune function such as HLA-Cw6, IL-12B, and IL-23R, provide valuable insights into the genetic underpinnings of psoriasis. Furthermore, genetic variants can influence the expression and activity of cytokines such as IL-17 and IL-23, contributing to individual differences in disease susceptibility and treatment response.[64]

To better understand and monitor these key immune markers in psoriasis, various molecular detection methods have been developed to track their expression and activity. For instance, Quantitative PCR (qPCR) assay allows the detection and quantification of mRNA expression of IL-17, IL-23, and TNFα in skin biopsies or peripheral blood, providing insight into the inflammatory status of the disease. Elevated levels of IL-17 and IL-23 have been consistently observed in the lesional skin of psoriasis patients, and these markers can be correlated with disease severity. By using specific antibodies against IL-17, IL-23, and TNFα, Immunohistochemistry (IHC) can visualize the spatial distribution and expression of these cytokines in psoriasis tissue samples.[63] This method allows researchers and clinicians to observe the localization of inflammatory cells in the skin and helps assess the degree of immune cell infiltration in psoriatic lesions. Flow cytometry can be used to analyze T-cell populations, specifically Th17 cells, in peripheral blood or skin tissue. By staining for surface markers such as CD4 and intracellular cytokines like IL-17, researchers can quantify Th17 cell subsets and assess their activation status.[64] This technique is also used in clinical trials to monitor the effect of targeted therapies that aim to modulate the IL-17/IL-23 axis. Enzyme-Linked Immunosorbent Assay (ELISA) is commonly employed to measure serum levels of TNFα, IL-23, and IL-17 in psoriasis patients, providing valuable biomarkers for assessing inflammation and monitoring therapeutic response. Elevated levels of these cytokines in serum have been associated with active disease, and their reduction can serve as a marker of therapeutic efficacy, particularly with biologic treatments.[65]

In conclusion, understanding the role of immune markers like TNFα, IL-23, and IL-17 in psoriasis pathogenesis is essential for developing targeted therapies. By utilizing molecular techniques such as qPCR, IHC, flow cytometry, and ELISA, clinicians and researchers can gain deeper insights into the disease mechanisms and improve the precision of diagnostics and treatment strategies. These advances will not only help elucidate the complexities of psoriasis but also enable more effective and personalized treatment approaches.

Genetic Contributions

Psoriasis has a strong genetic component, with monozygotic twins having a two- to threefold increased risk compared to dizygotic twins.[65,66] Genome-wide association studies (GWAS) have identified over 80 genetic loci explaining approximately 30% of the disease's heritability. While most variants have modest effects, they collectively illuminate the disease's

immunological underpinnings.[67,68] HLA-C06:02 is a key genetic risk factor for early-onset psoriasis, increasing risk four- to fivefold and interacting with ERAP1 to further elevate susceptibility. Although not yet therapeutically actionable, HLA-C06:02 may inform clinical and therapeutic stratification.[69,70] GWAS findings converge on innate and adaptive immune pathways, including type I interferons, NF-κB, IL-23, IL-17, and antigen presentation. These insights, coupled with immunological research, advance our understanding of psoriasis pathogenesis and inform therapeutic strategies.[71]

Triggers

Psoriasis expression is a result of complex gene-environment interactions, where environmental factors play a crucial role in triggering or exacerbating the disease in genetically predisposed individuals. While stress, infections (especially streptococcal), alcohol, smoking, and certain medications are well-established triggers, other factors, such as hormonal changes, allergies, irritants, and frequently consumed drugs, also contribute to the development or worsening of psoriasis. Each of these environmental triggers can influence immune system dysregulation, inflammatory pathways, or skin barrier function, which are central to psoriasis pathogenesis.[72]

Hormonal Changes

Hormonal fluctuations, particularly during puberty, pregnancy, and menopause, can significantly influence the onset and severity of psoriasis. Estrogen and progesterone levels, for instance, impact immune regulation and can alter the balance between pro-inflammatory and anti-inflammatory cytokines. During pregnancy, elevated estrogen levels can sometimes improve psoriasis symptoms, while in some cases, the disease may worsen postpartum due to rapid hormonal changes.[73]

For example, during pregnancy, elevated estrogen levels can sometimes improve psoriasis symptoms, while in some cases, the disease may worsen postpartum due to rapid hormonal changes. Besides, Menopause, with its decrease in estrogen, has been associated with a flare-up or onset of psoriasis in women who were previously asymptomatic. Androgens, which may rise in certain hormonal conditions (like polycystic ovary syndrome or hirsutism), may also influence psoriasis severity by stimulating keratinocyte proliferation and immune cell activation.[74] Hormonal changes may modulate the immune response, particularly through the regulation of Th1 and Th17 pathways, both of which play crucial roles in psoriasis pathogenesis. Estrogen, for example, can downregulate the Th17 response, while a reduction in estrogen during menopause can enhance this pathway, triggering an inflammatory cascade in genetically susceptible individuals.[75]

Allergies and Allergic Responses

Psoriasis can also be influenced by allergic reactions or heightened allergic sensitization, particularly to environmental allergens like pollen, dust mites, fungi, or pet dander. Additionally, food allergies or sensitivities (eg, to dairy or gluten) have been implicated in some patients with psoriasis, potentially exacerbating inflammation. For instance, Contact dermatitis from allergens like nickel or certain fragrances can provoke localized flares of psoriasis in sensitive individuals.[76] Type I hypersensitivity reactions (IgE-mediated) to airborne allergens might contribute to exacerbation of the disease through a systemic inflammatory response, particularly when the skin barrier is already compromised. Allergic reactions can trigger the release of histamine, prostaglandins, and cytokines such as IL-4, IL-5, and IL-13. These immune mediators can further activate T-helper cells, including Th2 cells, and promote the production of IL-17 and TNFα, both of which are key players in psoriasis pathogenesis.[77]

Irritants and Skin Trauma

Environmental irritants such as harsh soaps, chemicals, detergents, or abrasive fabrics can disrupt the skin barrier and trigger or worsen psoriasis lesions. Moreover, physical trauma (including cuts, scratches, sunburn, and even surgical procedures) can induce Koebner phenomenon, where new psoriatic lesions develop at sites of skin injury.[78] Skin damage can activate keratinocytes and mast cells, leading to the release of pro-inflammatory cytokines like IL-1 and TNFα, which stimulate T-cell activation and exacerbate the inflammatory process. Additionally, the Koebner phenomenon is thought to involve the activation of the innate immune system, with dendritic cells presenting self-antigens to T-cells, thus triggering an autoimmune response.[79]

Commonly Consumed Drugs

Certain medications are known to be psoriasis triggers, either by directly inducing or exacerbating the disease. Commonly used for hypertension, beta-blockers can exacerbate psoriasis by increasing the activity of TNFα and IL-6, which promote inflammation. Besides, used to treat bipolar disorder, lithium can trigger psoriasis or worsen existing symptoms by disrupting immune cell signaling and increasing the expression of IL-2 and TNFα.[80] In addition, Nonsteroidal anti-inflammatory drugs (NSAIDs), while effective for pain relief, may exacerbate psoriasis flares in some individuals by increasing the production of pro-inflammatory cytokines. Certain antibiotics, particularly penicillin and sulfonamides, can induce psoriatic flares, possibly due to their effect on the skin microbiome or immune system modulation. Medications like beta-blockers and lithium can influence immune cell function, especially by promoting the activity of T-helper (Th) 1/Th17 responses, which are central to psoriasis. These drugs may also alter the skin microbiome, increase systemic inflammation, or directly affect skin cell turnover, all contributing to disease exacerbation.[81]

Other Environmental Triggers

Infections, particularly streptococcal throat infections, can trigger guttate psoriasis in susceptible individuals. The immune system responds to the infection by activating the Th17 pathway, which can trigger or exacerbate psoriasis symptoms. Alcohol consumption, especially in excess, is known to provoke psoriasis flares, possibly by affecting immune function and increasing systemic inflammation.[82] Alcohol can also interact with medications, reducing their efficacy in treating psoriasis. Cigarette smoke contains numerous toxins that can contribute to systemic inflammation. Smoking increases the risk of developing psoriasis, and it is associated with more severe disease outcomes by promoting the Th1/Th17 immune response, as well as increasing oxidative stress and inflammatory cytokine production.[83]

Innate and Adaptive Immune System and Feed-Forward Amplification

T cells have been recognized as central to psoriasis pathogenesis since the 1980s, as evidenced by ciclosporin's efficacy.[84] While T cells are pivotal, other immune cells (dendritic cells, neutrophils, keratinocytes) also contribute. Epidermal hyperproliferation and the production of antimicrobial proteins, growth factors, and chemokines are driven by intercellular communication via cytokines and keratinocyte activation.[85] These factors perpetuate inflammation, inducing angiogenesis, neutrophil infiltration, and increased Th1 and Th17 cell numbers (Figure 3).

Tissue-resident memory T cells (TRM cells), non-circulating memory T cells residing in epithelial tissues, have garnered significant attention in recent years.[86] While evolved for rapid pathogen defense, TRM cell dysregulation contributes to immune-mediated diseases like psoriasis. Triggered by autoantigens, including HLA-C*06:02-presented antigens, TRM cell activation drives psoriasis pathogenesis.[87] The persistence of TRM cells in the skin explains disease characteristics like distinct lesion borders and recurrent involvement of previously affected sites.

Cytokine Circuits in Psoriasis: IL-23 and Th17 and Beyond

IL-23 and Th17 responses are central to psoriasis pathogenesis, as supported by GWAS and clinical trials. IL-23, a cytokine composed of p40 and p19 subunits, drives IL-17 production and T cell expansion.[85–87] Sharing the p40 subunit (ustekinumab target) with IL-12, which promotes Th1 responses and IFN-γ production, IL-23 has been successfully targeted therapeutically, unlike IL-12.[88–91]

The IL-17 cytokine family, which includes six members (IL-17A-F), is involved in psoriasis pathogenesis, with IL-17A being the most prominent.[92–94] IL-17C and IL-17F are also highly expressed, but their roles are less well-defined. Activated T cells and group 3 innate lymphoid cells are the primary sources of IL-17 in psoriatic plaques.[95–97] IL-17 upregulates CCL20, a Th17 chemoattractant, leading to a positive feedback loop.

TNFα, a proinflammatory cytokine produced by dendritic cells, macrophages, and T cells, exerts diverse biological effects.[98] These include inducing proinflammatory cytokine expression in dendritic cells and T cells, upregulating neutrophil chemoattractants, promoting vascular adhesion molecule expression for inflammatory cell influx, and amplifying cytokine effects, such as IL-17.[99]

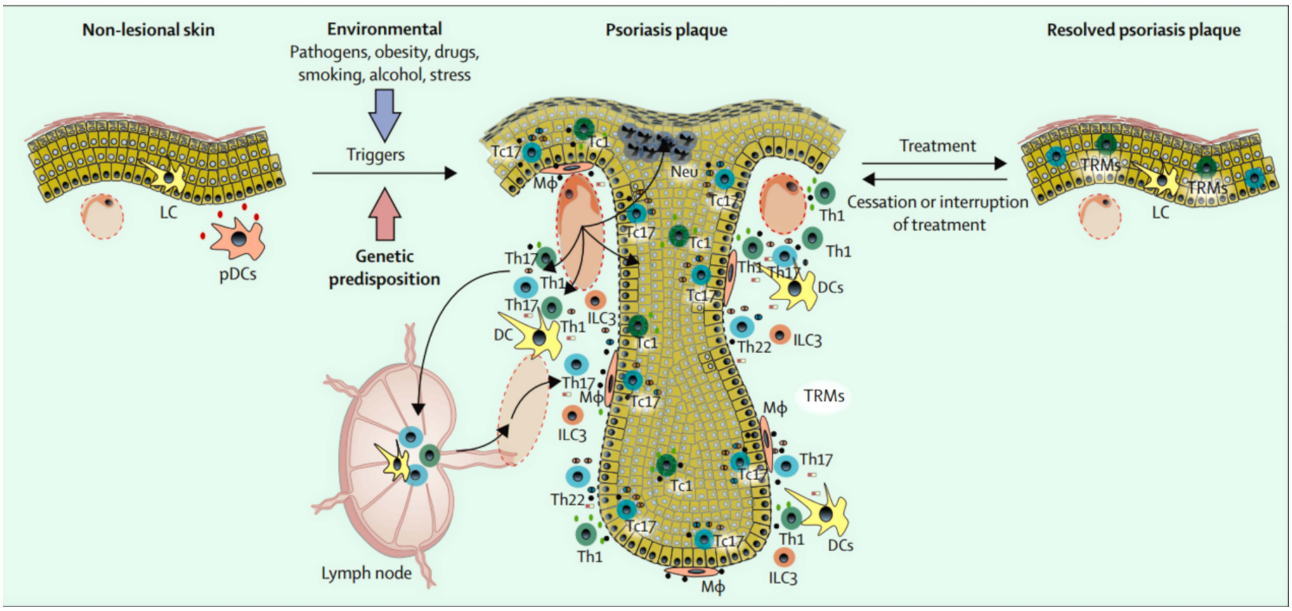

Figure 3 Immunopathogenesis of psoriasis and resolved psoriasis plaques. Psoriasis plaque development is a complex interplay between genetic susceptibility and environmental triggers, including but not limited to infections (eg, streptococcus), obesity, medications, alcohol, stress, and smoking. Over 80 genetic risk loci have been identified to date. In genetically predisposed individuals, these triggers initiate a cascade involving plasmacytoid dendritic cells and type I interferons, resulting in epidermal thickening (acanthosis), elongated rete pegs, and dilated dermal papillary blood vessels. The inflammatory process recruits various immune cells, including IL-17-producing group 3 innate lymphoid cells, Th17, and Tc17 cells; IFN-γ-producing Th1 and Tc1 cells; neutrophils; activated macrophages; and dendritic cells. Skin-draining lymph nodes amplify this response, creating a self-perpetuating inflammatory cycle. Resolved psoriasis plaques harbor tissue resident memory T cells (TRM), predominantly $CD8^+$ $IL\text{-}17^+$ or $CD8^+$ $IFN\text{-}\gamma^+$. Upon treatment interruption, these TRM reactivate, triggering recurrent inflammation at previous lesion sites. DC=dendritic cell; ILC=innate lymphoid cell; LC=Langerhans cell; Mφ=macrophage; Neu=neutrophil; pDC=plasmacytoid dendritic cell; Tc=cytotoxic T cell; Th=helper T cell.

IFN-γ, predominantly produced by T cells, was an early identified psoriasis plaque inflammatory mediator. IFN-γ, like type I interferons, exacerbates psoriasis by enhancing antigen processing, MHC class II expression on antigen-presenting cells, and the production of proinflammatory mediators, including the Th1 and Tc1 cell chemoattractants CXCL9 and CXCL10.[100–103]

The IL-36 cytokine family, consisting of IL-36α, IL-36β, IL-36γ, and IL-36 receptor antagonist (IL36RN), has recently gained attention.[104] IL36RN gene mutations are associated with pustular psoriasis, particularly generalized pustular psoriasis. Primarily expressed by epithelial cells, IL-36 cytokine expression is induced by proinflammatory cytokines such as IL-17, TNFα, and IL-36 itself.[104,105] This amplifies inflammation and neutrophil influx. Keratinocyte-secreted serine protease inhibitors, such as SERPINA3, regulate IL-36 activation. Loss-of-function SERPINA3 variants predispose to generalized pustular psoriasis.[106] CARD14 and AP1S3 gene mutations are also associated with pustular psoriasis, with CARD14 mutations linked to familial pityriasis rubra pilaris.[107]

The interplay between IL-23, IL-17, interferon, and IL-36 cytokine circuits influences psoriasis clinical manifestations.[108] In contrast to the predominance of IL-23 and IL-17 in plaque psoriasis, interferon responses are more pronounced in early-stage disease.[109] IL-36 is more involved in pustular forms. These circuits exhibit complex interdependencies, with IFN-γ boosting IL-23 and Th17 responses, and IL-17 stimulating IL-36 expression, creating a self-perpetuating inflammatory cycle[110] (Figure 4).

Disease Associations

Psoriasis frequently co-occurs with other diseases, most notably psoriatic arthritis, affecting 10–40% of patients.[111–113] Typically developing 10 years after psoriasis onset, psoriatic arthritis often presents asymmetrically, targeting distal interphalangeal joints, with potential axial involvement.[114,115] Enthesitis and dactylitis also characterize psoriatic arthritis. While sharing pathogenic and immunological features, psoriasis and psoriatic arthritis represent distinct genetic, immunological, and therapeutic entities.[116–118] While causality remains unclear, these conditions collectively increase morbidity in psoriasis patients. Lifestyle interventions, particularly weight management,[119–121] may improve outcomes,

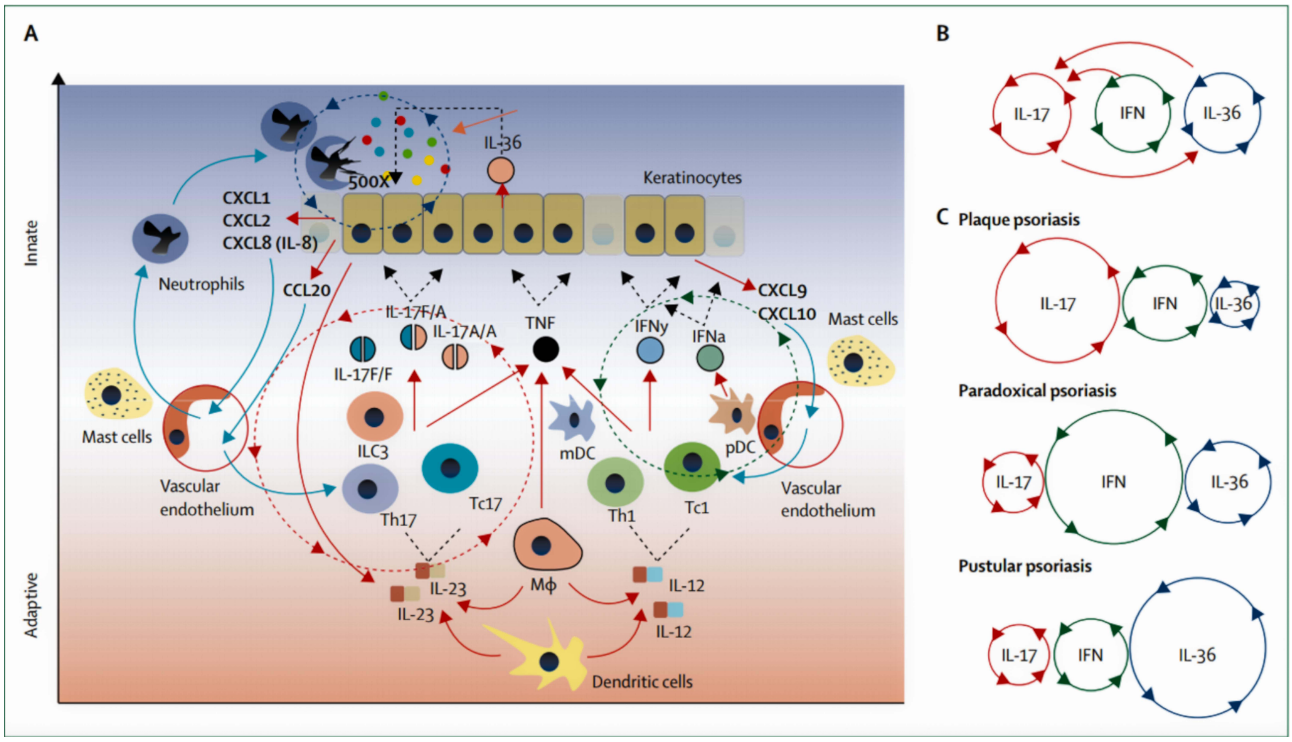

Figure 4 Inflammatory circuits in psoriasis. (**A**) Psoriasis skin inflammation is a complex interplay of adaptive and innate immunity, characterized by three interconnected circuits. An IL-17, IL-23, and CCL20 feedback loop drives Th17 and Tc17 responses (red dotted lines). A type I and II interferon circuit, initiated by plasmacytoid dendritic cells and IFN-γ-producing T cells (Th1 and Tc1), is regulated by CXCL9 and CXCL10 (green dotted lines). Lastly, an IL-36 and neutrophil axis, amplified by neutrophil chemokines CXCL1, CXCL2, and CXCL8 (IL-8), is central to the inflammatory response (blue dotted lines). Neutrophil proteases include cathepsin G (green), neutrophil elastase (blue), and proteinase 3 (red). (**B**) These circuits interact through positive feedback mechanisms, with IL-36 and IFN-γ responses enhancing Th17 activity and amplifying IL-36 production. (**C**) The clinical heterogeneity of psoriasis is linked to the balance of these circuits. Plaque psoriasis is dominated by IL-17 responses, while paradoxical psoriasis leans towards interferon responses and pustular psoriasis is characterized by IL-36 predominance. IFN=interferon; ILC=innate lymphoid cell; Mφ=macrophage; mDC=myeloid dendritic cell; pDC=plasmacytoid dendritic cell; Th=helper T cell; Tc=cytotoxic T cell.

as evidenced by reduced biologic therapy efficacy in obese psoriasis patients and beneficial effects of bariatric surgery on psoriasis.[122–124]

Management

Overall Treatment Strategy for Plaque Psoriasis

Psoriasis treatment strategies consider disease severity, psoriatic arthritis presence, comorbidities, and patient preferences.[125,126] For patients with psoriatic arthritis, systemic treatments addressing both conditions are prioritized. Treatment selection also reflects psoriasis severity, location, and associated medical conditions.[127,128]

Patient education is crucial, with resources available from organizations like the Psoriasis Association and National Psoriasis Foundation.[129] A holistic management approach emphasizes lifestyle modifications. Programs like PsoWell, incorporating motivational interviewing, have proven beneficial.[130] While individual educational sessions are effective, resource limitations may hinder their widespread implementation.[131]

Treatment Goals

European guidelines typically stipulate that a body surface area involvement of more than 10%, a psoriasis area severity index (PASI) score of 10 or higher, or a dermatology life quality index score exceeding 10 is necessary.[132,133] Alternatively, the condition can be defined by significant physical, social, or psychological impact, depression or anxiety, or treatment-resistant localized psoriasis with dysfunction.[134–136] The International Psoriasis Council advocates a dual-therapy approach for moderate-to-severe psoriasis, with topical and systemic therapies as the two main options.[137] Systemic therapy is indicated for body surface area involvement exceeding 10%, psoriasis affecting specific sites, or

inadequate topical therapy response.[138] While step therapy (phototherapy followed by oral agents and biologics) was previously common, current guidelines often consider biologics, oral agents, and phototherapies concurrently.[139]

In the UK, eligibility for biologic or oral small molecule therapies is based on the criteria set by the National Institute for Health and Care Excellence. Patients must have had plaque psoriasis for a minimum of six months, with a PASI score of 10 or higher, a DLQI score exceeding 10, and must have shown inadequate response to or intolerance of conventional systemic treatments such as methotrexate.[137]

Important and measurable disease endpoints for the management of psoriasis are continually developing, considering factors like disease severity, patient impact, and treatment response. A treat-to-target approach focusing on disease control and improved outcomes is gaining global momentum. Attaining a psoriasis area severity index (PASI) of 2 or lower, a physician's global assessment indicating clear or nearly clear skin (which corresponds to a 90% reduction in PASI), and a dermatology life quality index (DLQI) score below 5 are achievable treatment objectives.[138]

Topical Therapy

Liberal emollient use is essential for all psoriasis patients. Localized psoriasis (affecting <3-5% of body surface) is typically managed with topical agents like corticosteroids, vitamin D3 analogs, and combination formulations. Targeted phototherapy is also an option. While crude coal tar and dithranol remain available in specialized settings, newer, more cosmetically appealing alternatives are preferred. Adherence to topical therapies often proves challenging.[138]

Phototherapy

Ultraviolet radiation has local immunosuppressive effects that specifically affect Langerhans cells, reduce epidermal hyperproliferation and angiogenesis, and promote T cell apoptosis. Various phototherapy options include narrowband ultraviolet B radiation (311–313 nm), broadband ultraviolet B radiation (280–320 nm), targeted phototherapy, and, though less frequently used due to the potential risk of skin cancer, oral psoralen ultraviolet A (PUVA). Narrowband ultraviolet B, administered two to three times weekly, is the most common modality, with home units gaining popularity. While effective for plaque psoriasis, narrowband ultraviolet B can cause burning and carries a lower photocarcinogenesis risk compared to PUVA. Some centers still combine narrowband ultraviolet B with crude coal tar or dithranol.[139]

Oral Systemic Therapies

Prior to the advent of biologics, oral systemic agents were the mainstay for treating moderate-to-severe plaque psoriasis. These medications exhibit a variety of mechanisms of action, effectiveness, and safety profiles (Table 1). Targeting ubiquitous intracellular targets, these small molecules often have broader effects than biologics. Frequently used oral agents comprise methotrexate, ciclosporin, acitretin, fumarates, and apremilast. Additionally, a TYK2 inhibitor is presently in the later stages of development.[140]

Methotrexate has been utilized in the treatment of psoriasis and psoriatic arthritis for more than 50 years. Its mechanism of action is thought to involve the inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide transformylase and the production of adenosine, which suppresses lymphocyte activity.[141] Administered weekly, methotrexate

Table 1 Recognized Topical Psoriasis Therapies

Active Substance	Pharmacological Activity	Side Effects
Skin conditioners	Decreases hyperproliferation, promotes proper differentiation, and prevents excessive cell apoptosis. Additionally, it offers anti-inflammatory benefits and enhances barrier function.	Allergic contact dermatitis, fragrance sensitivity, skin stinging, and acne formation.
Bituminous tar	Inhibits DNA synthesis, thereby decreasing the excessive proliferation of keratinocytes.	Odor, staining, irritant dermatitis, redness, stinging sensation, folliculitis, and development of keratoacanthomas.

(*Continued*)

Table 1 (Continued).

Active Substance	Pharmacological Activity	Side Effects
Ortho-hydroxybenzoic acid	Decreases the cohesion between horny cells by breaking down the intercellular binding material. Additionally, it lowers the pH of the stratum corneum, enhancing moisture retention and softening the skin.	Possible acute or chronic systemic toxicity, oral mucosal burning, frontal headache, central nervous system effects, metabolic acidosis, ringing in the ears, nausea, and vomiting.
TCAs	It blocks the activity of calcineurin phosphatase and prevents the production of inflammatory compounds believed to play a key role in the development of skin lesions.	Burning sensation and skin discomfort.
Topical retinoid	It attaches to β and γ retinoic acid receptors on the keratinocyte cell membrane, before being transported to the nucleus, where it modulates gene transcription in keratinocytes.	Localized discomfort
Cignolin	It decreases keratinocyte proliferation, inhibits T-cell activation, and promotes normal cell differentiation, likely by inducing mitochondrial dysfunction.	Skin irritation, along with staining of affected areas, surrounding skin, hair, nails, clothing, and other objects that come into contact with the patient.
Topical steroid medications	Corticosteroids possess vasoconstrictive, antiproliferative, anti-inflammatory, and immunosuppressive properties. They attach to the intracellular corticosteroid receptor and modulate the transcription of various genes, especially those involved in the production of proinflammatory cytokines.	Skin thinning, stretch marks, telangiectasia, and secondary infections are potential side effects. As a result, potent TCS should be avoided on the face or areas with skin folds. Systemic side effects may arise when TCS are used for extended periods or at higher doses than typically recommended. Long-term use of strong TCS can lead to significant systemic absorption, potentially causing HPA axis suppression, Cushing's syndrome, and elevated blood sugar levels.
1,25-dihydroxyvitamin D analogues	Vitamin D analogues interact with the intracellular Vitamin D receptor, which subsequently binds to and modulates the genes that control epidermal proliferation, inflammation, and keratinization.	Skin irritation, elevated calcium levels, increased calcium excretion in urine and suppression of parathyroid hormone are potential side effects, though these occur very infrequently.

Abbreviations: TCAs, Topical calcineurin antagonists; TCS, topical corticosteroids.

primarily causes bone marrow suppression, with liver fibrosis risk. Non-invasive techniques for assessing liver fibrosis include measuring serum levels of the amino propeptide fragment of procollagen III, elastography, and using algorithm-based risk assessments. Additional side effects may consist of nausea, vomiting, hair loss and teratogenic effects. Folic acid supplementation is recommended to mitigate hematological and gastrointestinal adverse effects.[142]

Subcutaneous methotrexate, increasingly replacing oral administration in some countries, offers potential advantages in efficacy, bioavailability, and gastrointestinal tolerability. While methotrexate can be combined with anti-TNFα biologics to reduce antidrug antibody development, this practice is more common in rheumatology than dermatology.[143]

Ciclosporin, a systemic calcineurin inhibitor, is indicated for short-term treatment of severe plaque psoriasis or for managing crises, in addition to serving as a bridge to long-term therapies. Rapid onset and robust efficacy characterize ciclosporin, but its use should not exceed one year due to nephrotoxicity risk. Other side effects may involve hypertension, increased risk of infections, nausea, excessive hair growth, gingival hyperplasia, interactions with other medications, and imbalances in electrolytes.[144]

Acitretin, a synthetic retinoid used systemically, treats severe plaque psoriasis by regulating keratinocyte proliferation and providing immunomodulatory effects. While also used for pustular psoriasis and palmoplantar psoriasis, acitretin's use in plaque psoriasis has declined. Its use is not recommended for women of childbearing age because of its potential teratogenic effects.[145]

Fumaric acid esters are small molecules that inhibit the maturation of dendritic cells, promote T cell apoptosis, and disrupt leukocyte extravasation. They are commonly utilized in Germany for treating moderate to severe plaque psoriasis. Dimethyl fumarate, a formulation of a single ester, has received approval from the European Medicines Agency. Gradual dose escalation is necessary due to frequent flushing and diarrhea (affecting up to 40% of patients). Lymphocytopenia below 0.8 K/μL necessitates dose reduction to mitigate progressive multifocal leukoencephalopathy risk.[146]

Apremilast, which acts as a phosphodiesterase-4 inhibitor, is used to manage moderate to severe psoriasis and psoriatic arthritis. Its immunomodulatory properties reduce proinflammatory cytokines such as TNFα, IL-2, and IL-12, while enhancing the levels of the anti-inflammatory cytokine IL-10. Frequent side effects include nausea, diarrhea, and weight loss.[147]

Biological Treatment

In the past two decades, biologic therapies have significantly transformed the treatment of psoriasis and psoriatic arthritis. These therapies primarily consist of recombinant monoclonal antibodies or receptor fusion proteins, which can be fully human, humanized, or human–mouse chimeric, and are designed to target specific inflammatory mediators.[148] While they are currently categorized as immunosuppressants, it is becoming increasingly clear that drugs targeting highly specific immune pathways cannot be simply classified as either suppressive or stimulatory.[149] Therefore, a new classification system is needed to better describe the modulatory effects of these drugs, which is particularly important for identifying patients at increased risk of infections. All biologics for psoriasis, except infliximab, are administered via subcutaneous injection.[150] Currently, there are 11 biologic treatments across four distinct classes—anti-TNFα, anti-IL-17, anti-IL-12p40 or IL-23p40, and anti-IL-23p19—used for managing moderate-to-severe psoriasis.[151]

Currently, four anti-TNFα agents are approved for the treatment of psoriasis: adalimumab, certolizumab pegol, etanercept, and infliximab. Etanercept is a fusion protein combining tumor necrosis factor receptor 2 (TNFRSF1B) with the Fc region of IgG1.[152] Certolizumab pegol, on the other hand, is a monoclonal antibody fragment conjugated with polyethylene glycol, a modification that reduces immunogenicity, extends its half-life, and prevents it from crossing the placental barrier. Adalimumab is a fully human monoclonal antibody, while infliximab is a chimeric antibody.[153] Additionally, a fifth anti-TNFα agent, golimumab, is approved for psoriatic arthritis but has not yet been approved for psoriasis treatment.

Three anti-IL-17 therapies have been approved: secukinumab, ixekizumab, and brodalumab. Secukinumab and ixekizumab both specifically target IL-17A, while brodalumab inhibits the IL-17 receptor A (IL-17RA), blocking IL-17A, IL-17F, and additional cytokines in the IL-17 family, including IL-17C and IL-17E (also known as IL-25). Bimekizumab, which targets both IL-17A and IL-17F, is currently undergoing Phase 3 clinical trials for psoriasis.[154]

Currently, four IL-23-targeting agents are approved for psoriasis treatment: ustekinumab, which inhibits the shared p40 subunit of IL-12 and IL-23, and guselkumab, risankizumab, and tildrakizumab, which specifically target the p19 subunit of IL-23.[155] Another anti-IL-23p19 biologic, mirikizumab, is undergoing phase 3 clinical trials (NCT03482011 and NCT03535194). IL-23 plays a crucial role in sustaining and amplifying Th17 and Tc17 cell responses. The suppression of IL-17 activity is believed to be the primary mechanism driving the therapeutic effectiveness of these treatments.[156]

The highly targeted nature of biologic therapies can sometimes paradoxically trigger inflammatory responses, leading to disease worsening and shifts in clinical and immunological characteristics. A well-documented example of this phenomenon is the development of psoriasis or a worsening of existing psoriasis during anti-TNFα or anti-IL-6 therapy.[157] This adverse reaction is more prevalent in women and often manifests as palmoplantar pustulosis. Another notable shift is the transformation of psoriasis into atopic dermatitis-like features, characterized by morphological changes, pruritus, and eosinophilia. This transformation has been observed with various biologics but is particularly prominent with anti-IL-17 and anti-IL23p19 therapies.[158] Although highly effective for many, biologic therapies exhibit varying responses among patients. Some individuals may not respond at all (primary failure), while others may initially respond but subsequently lose efficacy (secondary failure). Factors such as non-adherence, low drug concentrations due to anti-drug antibody development, high body mass index, and sex differences have been implicated in these outcomes.[155] Notably, men tend to have better initial responses and maintain therapeutic efficacy longer than women.[156]

The introduction of low-cost biosimilars following the expiration of biologics' patents has made these treatments more accessible. Numerous biosimilars of infliximab, etanercept, and adalimumab are now available, offering significant cost savings in high-income countries while potentially enabling patients in low- and middle-income countries to access treatment.[157] The true safety and, to a lesser extent, the efficacy of biologics for psoriasis can only be fully understood through real-world evidence gathered from long-term pharmacovigilance registries, such as the British Association of Dermatologists Biologics and Immunomodulators Register (UK), PsoBest (Germany), and BIOBADADERM (Spain).[158] So far, the data are reassuring, demonstrating a generally favorable safety profile for biologics without major concerns regarding infection or cancer risk, provided that the required pretreatment and annual screening protocols are followed.[159]

Other Marketed Therapies

Psoriasis, a chronic condition, often necessitates long-term management. Treatment options vary widely based on disease severity, comorbidities, and individual responses. Psoriasis severity is graded using metrics like lesion severity, affected skin area, and quality of life.[35] Psoriasis is classified into mild, moderate, and severe categories, taking into account factors such as the severity of lesions and the extent of skin involvement. Around 80% of individuals with psoriasis have mild to moderate forms, which are usually treated with topical therapies.[36,37] Moderate cases often require a combination approach, including corticosteroids and other topical agents such as vitamin D derivatives.

Vitamin D3 analogs serve as the main topical therapy for plaque psoriasis and moderately severe cases affecting the scalp.[38,39] The therapeutic advantages of vitamin D obtained from sunlight exposure in managing psoriasis have been acknowledged for many years.[40–42] Nonetheless, the function of vitamin D in psoriasis and various other skin disorders is still intricate and subject to debate.[43,44] Filoni et al helped shed light on this matter by demonstrating that psoriatic patients tend to have lower levels of vitamin D, which are associated with the duration of the disease.[45] Lee et al further supported these findings by identifying decreased 25-hydroxyvitamin D (25OHD) levels, a marker of vitamin D stores, in psoriasis patients.[46,47] Nevertheless, the correlation between increased 25OHD levels following phototherapy and improved psoriasis severity remains inconclusive.[48]

Vitamin D plays a crucial role in keratinocyte proliferation (Figure 5). Its precursor, 7-DHC, undergoes UV-induced conversion to cholecalciferol, subsequently transformed into the active form, calcitriol, via intermediate 25OHD.[48–52] Calcitriol modulates keratinocyte differentiation, proliferation, and immune balance, exerting both stimulatory and inhibitory effects based on concentration.[43] Through calcium regulation, calcitriol and its analogs demonstrate therapeutic potential. In vitro studies reveal their ability to reduce psoriatic S100A7 levels, modulate keratinocyte proliferation, and regulate glycoceramides. Calcitriol deficiency or receptor dysfunction disrupts epidermal homeostasis, leading to basal layer hyperproliferation.[43] Vitamin D's anti-inflammatory actions include suppressing IL-2 production. Additionally, calcitriol and novel vitamin D3 derivatives suppress NF-κB, a key inflammation mediator.[41]

Although multiple studies associate vitamin D receptor (VDR) polymorphisms with susceptibility to psoriasis, this connection is still a topic of controversy.[43,53,54] The activated vitamin D receptor (VDR) forms a complex with the retinoid X receptor (RXR), which attaches to vitamin D response elements (VDREs) to modulate gene expression. This genomic action contrasts with vitamin D's direct influence on signaling pathways (nongenomic action).[38] VDR gene variations can impact treatment response, with VDR isoform A linked to improved outcomes in psoriatic patients.[43] VDR ligands suppress T cell-derived proinflammatory cytokines, while 1α,25(OH)2D3 increases the expression of IL-10 in psoriatic lesions. Vitamin D3 analogs inhibit T cell-mediated immune responses.[41] Additionally, CYP11A1-synthesized 20(OH)D3 exhibits anti-proliferative, pro-differentiation, and anti-inflammatory properties, comparable to or surpassing 25OHD. This metabolite holds promise as a novel therapy for hyperproliferative and inflammatory conditions, including psoriasis.[55]

Beyond the classic vitamin D activation pathway, alternative routes involving CYP11A1 have emerged. Traditionally linked to steroidogenesis in specific organs, CYP11A1 catalyzes cholesterol conversion to pregnenolone through sequential hydroxylations and cleavage.[55] Recent findings expand CYP11A1's substrate range to include 7-DHC, vitamins D2, and lumisterol.[56] CYP11A1 initiates vitamin D metabolism, primarily producing 20(OH)D3, along with

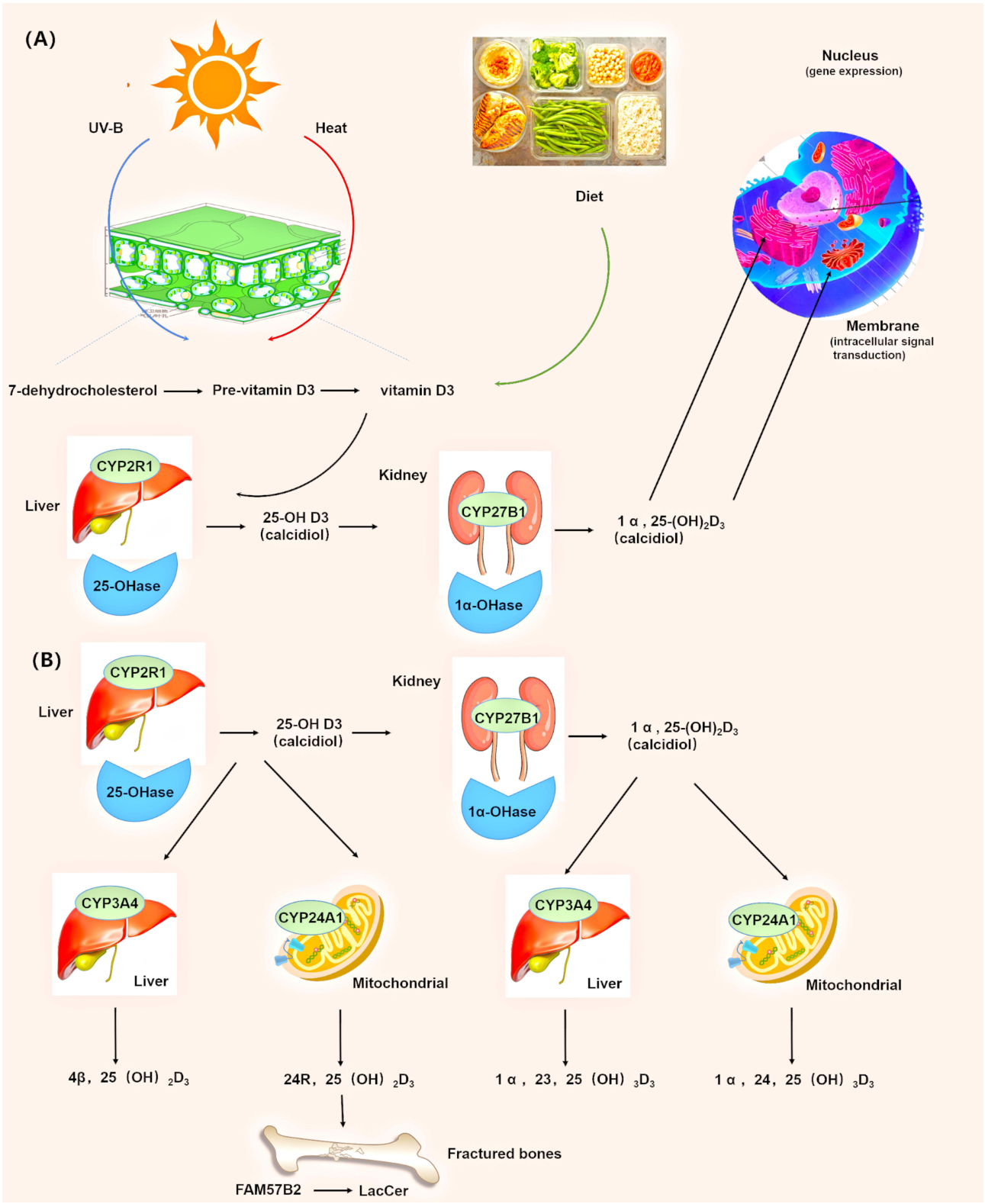

Figure 5 The physiological pathway of vitamin D synthesis and activation.(**A**) Vitamin D is produced in the skin through UV-induced conversion of 7-dehydrocholesterol to pre-vitamin D, which isomerizes to vitamin D3 (cholecalciferol). Alternatively, vitamin D2 (ergocalciferol) can be obtained from dietary supplements. The liver converts vitamin D into 25-hydroxyvitamin D (25(OH)D3) via CYP2R1. Subsequently, the kidney transforms 25(OH)D3 into the active hormone 1α,25-dihydroxyvitamin D3 (1,25 (OH)2D3) using CYP27B1. This active form enters cells through diffusion or endocytosis and binds to vitamin D receptors (VDRs) located in both the nucleus and cell membrane. Nuclear VDRs form a regulatory complex initiating transcription, while membrane VDRs trigger intracellular signaling. (**B**) An alternative pathway involves additional cytochromes. CYP3A4, predominantly in the liver, accelerates vitamin D inactivation, while CYP24A1, primarily in mitochondria, produces the active metabolite 24R,25(OH)2D3. This molecule binds to FASN57B2 in fractured bones, stimulating lactosylceramide (LacCer) production essential for callus formation and fracture healing.

minor 22(OH)D3 and 17(OH)D3 metabolites.[57] Subsequent CYP11A1-mediated hydroxylations generate dihydroxy and trihydroxy metabolites, including 20.23(OH)2D3 and 17,20,23(OH)3D3.[58]

Beyond the classic VDR-mediated genomic mechanism, vitamin D elicits rapid nongenomic effects through alternative binding sites. The VDR's A-pocket and the membrane-bound receptor PDIA3 facilitate these responses. PDIA3, a rapid steroid binding protein, activates phospholipase C via a G protein-coupled mechanism, leading to IP3 and diacylglycerol production and subsequent calcium release.[59] Additionally, vitamin D targets RORγ, another nuclear receptor, where hydroxyderivatives act as antagonists, influencing immune function and cerebellar development.[59,60]

Severe psoriasis often necessitates systemic therapy, sometimes in conjunction with topical treatments. To enhance topical efficacy, adjunctive therapies like penetrating enhancers or phototherapy can be considered.[61] Monotherapy regimens, requiring inconsistent application, often hinder treatment adherence.[62] Combination therapies, offering fixed dosing and reduced application frequency, represent a more effective approach to improving patient compliance.[63,64]

Topical treatments are fundamental in managing psoriasis, providing safety and good tolerability. Mild plaque psoriasis is often treated with a combination of vitamin D derivatives and betamethasone, whereas topical calcineurin inhibitors (TCIs) and vitamin D analogs are commonly recommended for different subtypes of psoriasis. TCIs serve as steroid-sparing agents in inverse psoriasis, and tazarotene excels as a maintenance therapy (Table 1). Innovative vehicle formulations enhance topical delivery, addressing adherence, penetration, and application site-specific needs, thereby improving patient compliance.[78] Emerging target-based agents and nanotechnology promise to further optimize efficacy, adherence, and penetration while minimizing side effects. While topical therapy remains the mainstay for mild to moderate psoriasis, long-term data on these treatments remain limited. Severe psoriasis necessitates a range of treatments, from topical agents to systemic therapies, each with varying efficacy and safety profiles. All these systemic medications are approved for psoriasis. Studies consistently demonstrate superior PASI 90 rates with biologics compared to small-molecule therapies (Table 2).

Despite advancements in systemic psoriasis treatments, patient response variability and treatment limitations persist. Issues such as low drug absorption and potential toxicity hinder treatment efficacy and reproducibility. Ongoing research

Table 2 Authorized Systemic Interventions

Therapeutic Approach	Substance	Pharmacological Activity	Side Effects
Conventional therapy	Acitretin	It attaches to nuclear receptors that regulate genes responsible for cell differentiation, anti-proliferative effects, anti-inflammatory actions, anti-keratinization, and suppression of neutrophil chemotaxis. It is the only systemic therapy that does not suppress the immune system.	Depression, elevated triglycerides and cholesterol, muscle pain, chapped lips, skin peeling, hair loss, dry skin, nasal inflammation, nail changes, nosebleeds, sticky skin, retinoid-induced dermatitis, and dry eyes.
	Fumaric acid derivatives	It possesses immunomodulatory, anti-inflammatory, and antiproliferative effects, along with inducing apoptosis in activated T cells.	Facial warmth, redness, headaches, proteinuria, temporary kidney insufficiency, microscopic blood in the urine, and proximal tubular damage.
	Ciclosporin	It blocks the synthesis of interleukins like IL-2 and prevents T cell differentiation.	High blood pressure, arrhythmia, anxiety, headaches, fever, low magnesium levels, elevated potassium, abnormal lipid levels, and encephalopathy.
	Amethopterin	It decreases IL-17 mRNA and protein expression in peripheral blood mononuclear cells stimulated by CD3 and CD28. Additionally, it regulates pro-inflammatory mediators and influences atherogenic gene expression in psoriatic lesion skin.	Digestive upset, stomach cramps, and diarrhea

(*Continued*)

Table 2 (Continued).

Therapeutic Approach	Substance	Pharmacological Activity	Side Effects
Small molecules	PDE4 inhibitor	It suppresses the expression and/or production of TNF-α, IFN-γ, IL-12, IL-23, and chemokines such as CXCL9, CXCL10, CCL2, and CCL3. Additionally, it reduces IL-2, IL-5, IL-13, IL-17, TNF-α, and IFN-γ production in stimulated T cells, as well as IFN-α in dendritic cells.	Vomiting sensation, digestive upset, and head discomfort
Small molecules	Tofacitinib	It is a powerful inhibitor of JAK1 and JAK3, with some effect on JAK2 and Tyk2.	Common side effects include nasopharyngitis, upper respiratory infections, headaches, urinary tract infections, and diarrhea.
Anti-TNF alpha	Remicade	It disrupts TNF-α activity by directly binding to both soluble and membrane-bound TNF-α molecules in the plasma and affected tissues.	Labored breathing, rash, decreased blood pressure, skin redness, and head discomfort
	Etanercept	It is a recombinant human TNF receptor delivered via subcutaneous injection. This fusion protein counteracts the effects of endogenous TNF by competitively blocking its interaction with cell surface receptors.	Respiratory illnesses, flu-like symptoms, and digestive issues.
	Adalimumab	It prevents its binding to the p55 and p75 TNF receptors on the cell surface.	The most common side effects include headache, nausea, increased triglycerides, cough, sinus congestion, and fatigue.
	Certolizumab	It prevents lipopolysaccharide-induced IL-1β release from monocytes and induces non-apoptotic cell death in cells expressing TNF-α.	It blocks lipopolysaccharide-induced IL-1β release from monocytes and triggers non-apoptotic cell death in cells that express TNF-α.
Anti-IL12/23	Stelara	It is a human monoclonal antibody that specifically binds to the shared p40 protein subunit of interleukins 12 and 23, preventing their interaction with the IL12Rβ1 receptor on cell surfaces.	Cephalalgia, common cold, joint aches, and upper respiratory symptoms
Anti-IL17	Secukinumab	It is a fully human, high-affinity recombinant IgG1κ monoclonal antibody that specifically binds to and neutralizes interleukin-17A.	Common side effects include nasal inflammation, headaches, and upper respiratory infections.
	Bimekizumab	It is an immunoglobulin G1 monoclonal antibody, specifically engineered to bind to similar sites on both IL-17A and IL-17F, thereby achieving dual inhibition of these isoforms.	Upper respiratory inflammation, throat discomfort, and cephalalgia
	Ixekizumab	It is a humanized IgG4-κ monoclonal antibody with high affinity that specifically binds to and neutralizes IL-17A, a key proinflammatory cytokine produced by Th17 cells.	Nasal inflammation, cold-like symptoms, injection area discomfort, and headache
IL17R antagonist	Brodalumab	It binds with high affinity to human interleukin-17RA, inhibiting the biological activities of interleukins 17A, 17F, the 17A/F heterodimer, and 17E.	Nasal inflammation, respiratory tract infection, joint pain, and redness at the injection site.

(*Continued*)

Table 2 (Continued).

Therapeutic Approach	Substance	Pharmacological Activity	Side Effects
Anti-IL23	Tildrakizumab	It is a new, high-affinity humanized IgG1/j monoclonal antibody that selectively targets the p19 subunit of human IL-23, while not interacting with IL-12.	Cold-like symptoms and cephalalgia
	Guselkumab	It is a fully human IgG1 lambda monoclonal antibody that specifically targets the p19 subunit of IL-23.	Nasal inflammation and respiratory tract infection.
	Risankizumab	It is a humanized IgG1 monoclonal antibody that targets the p19 subunit of IL-23, thereby blocking this crucial cytokine and its involvement in psoriatic inflammation.	Respiratory tract infection, urinary tract infection, flu, and head pain.
	Mirikizumab	It is a humanized IgG4 variant monoclonal antibody that specifically targets the p19 subunit of IL-23, without binding to IL-12.	Viral infections of the upper and other parts of the respiratory tract, pain at the injection site, high blood pressure, and diarrhea.

Abbreviations: IL-17A, interleukin 17A; Th17, type 17 helper T.

focuses on identifying novel drug candidates and biosimilars.[100] Additionally, exploring alternative drug delivery methods, including microneedles and nanotechnology, is a growing area of interest.

Clinical Trials

Intensive research over the past decade has yielded significant advancements in psoriasis pharmacotherapy, encompassing both biologics and novel small molecules. A diverse pipeline of drugs, administered topically or orally, is currently undergoing clinical evaluation. These promising candidates have the potential to expand the therapeutic armamentarium for psoriasis.[148] Notably, several new agents with various delivery methods are in late-stage development and may receive regulatory approval in the near future (Table 3).

Topical administration remains the primary route for psoriasis treatment, particularly in mild to moderate cases. Ongoing efforts focus on developing novel topical formulations and active ingredients to enhance therapeutic outcomes. Numerous topical drug candidates are currently under clinical investigation. While parenteral delivery, especially subcutaneous administration, has gained prominence for biologics, oral formulations are the predominant focus of current clinical trials.[149]

Table 3 Innovative Psoriasis Treatments Currently Being Tested in Clinical Trials

Clinical Trial Phase	Drug Name	Administration Via	Targeting
Phase I	BOS-475	Topical	Bromodomain and extraterminal domain protein inhibitors
	ABBV-157	Oral	RORγt inhibitor
	CC-92252	Oral	Interleukin-2 receptor agonists; Regulatory T-lymphocyte stimulants
	EDP 1066	Oral	Immunomodulators
	EDP 1815	Oral	Immunomodulator

(*Continued*)

https://doi.org/10.2147/JIR.S506103

Table 3 (Continued).

Clinical Trial Phase	Drug Name	Administration Via	Targeting
Phase II	ABY-035	Parenteral	IL-17A inhibitor
	ARQ-151	Topical	PDE4 Enzyme inhibitor
	BI 730357	Oral	Nuclear receptor antagonist
	EISO	Topical	PDE4 blocker
	JTE-451	Oral	ROR inhibitor
	M1095	Parenteral	Trivalent monomeric nanobody that neutralizes interleukins IL-17A, IL-17F, and IL-17A/F
	PF-06700841	Topical	JAK1 and TYK2 inhibitor
Phase II	PF-06826647	Oral	TYK2 inhibitor
	SHR-1314	Parenteral	IL-17A Antagonist
Phase III	BMS- 986165	Oral	Tyk2 inhibitor
	BCD-085	Parenteral	IL-17 inhibitor
	BI695502	Parenteral	TNF-α inhibitor
	CF101	Oral	Adenosine A3 receptor inhibitor
	CHS-1420	Parenteral	TNF-α inhibitor
	Filgotinib	Oral	JAK 1 inhibitor
	Mirikizumab	Parenteral	IL-23 inhibitor
	Serlopitant	Oral	Neurokinin-1 receptor antagonist
	Tapinarof	Topical	AHR agonist
	Tildrakizumab	Parenteral	IL-23 inhibitor
	Upadacitinib	Oral	JAK inhibitor

Nanotechnology Applications in Psoriasis Management

The past two decades have witnessed a nanotechnology revolution, with intense focus on developing novel medical treatments. The technology's versatility enables the use of diverse materials with tailored properties. While nanoparticles often serve as drug carriers, biodegradable variants hold particular promise for psoriasis therapy.[150]

Polymeric Nanoparticles (PNPs)

Polymer-based nanoparticles (PNPs) excel as biomaterials due to their biocompatibility, versatile size and structure, biomimetic properties, and ease of modification. This versatility enables targeted drug delivery. The PNP family encompasses a wide range of structures beyond nanospheres and nanocapsules, including dendrimers and micelles.[151]

Nanospheres

Nanospheres encapsulate drugs within a polymer matrix.[120] Whether biodegradable or non-biodegradable, their primary functions are to enhance drug solubility.[126] Gel composition significantly influenced nanosphere dispersion, with METHOCEL™ K15M0 (HPMC) providing superior homogeneity compared to Carbopol. Optimal dispersion occurred at a 3 mg/mL tyrosphere concentration in HPMC, yielding ~40 nm particles. Diering et al explored tyrospheres for

vitamin D3 delivery, achieving an average particle sizes between 64.3 and 73.4 nm relying on vitamin D3 concentration.[127] Enhanced drug absorption with increased vitamin D3 levels was observed compared to controls.

Nanocapsules

Nanocapsules encapsulate drugs within a polymer shell. The core may contain an oily phase, a polymer matrix, or molecularly dispersed drug. These systems offer advantages including sustained release, improved drug selectivity, bioavailability, and reduced toxicity.[128,129] Marchiori et al developed dexamethasone-loaded nanocapsules for topical delivery.[130] A capric triglyceride core and polycaprolactone shell, embedded in Carbopol gel, yielded 201 nm particles with >95% encapsulation efficiency. In vitro studies demonstrated controlled drug release and stability, warranting further in vivo investigation.

Dendrimers

Dendrimers, spherical, monodisperse, multivalent macromolecules, offer unique properties including solubility, biocompatibility, and reactivity.[131] Drug delivery can occur through encapsulation or covalent conjugation, protecting against degradation. Their structure allows for diverse release mechanisms.[132] Agrawal et al investigated polypropyleneimine dendrimers for dithranol delivery, achieving 8 nm particles with drug loading upon dendrimer exposure to dithranol.[133] Drug permeation increased from 35% to 95%, and skin irritation decreased compared to dithranol solution. These findings highlight dendrimers as promising drug delivery candidates.

Micelles

Micelles, formed by amphiphile self-assembly above the critical micelle concentration, possess a hydrophobic core and hydrophilic shell. This structure protects hydrophobic drugs, enhancing solubility, bioavailability, and circulation time.[152] Micelles offer advantages like high drug loading, reduced degradation, and potential for decreased side effects, making them attractive for topical skin disease treatments. Lapteva et al investigated MPEG-dihex PLA micelles for tacrolimus delivery, achieving sub-50 nm particles.[135] While tacrolimus's poor water solubility made micelles promising, in vivo studies revealed skin surface retention without stratum corneum penetration, limiting their transdermal delivery efficacy compared to other systems.

Lipid-Based Nanoparticles

Lipid nanoparticles, made from natural physiological lipids, provide a safe and non-toxic option for various applications. Their unique structural composition brings numerous benefits, such as improved stability of the drugs they carry, extended circulation time within the body, and the ability to degrade naturally. Additionally, these nanoparticles possess targeting capabilities that allow for precise delivery of therapeutic agents to specific sites, while also facilitating a high drug loading capacity at competitive costs. This combination of features makes lipid nanoparticles an attractive choice in the development of effective treatment strategies.[136,137]

Liposomes

Liposomes are round vesicles formed by one or more layers of lipid bilayers that encapsulate water-filled compartments.[136,138] Their ability to solubilize insoluble drugs, act as local drug depots, and enhance the penetration of poorly soluble molecules into the stratum corneum makes them a focus for dermatological treatments. Liposome physicochemical properties, including charge, size, permeability, and stability, are readily adjustable, offering versatility in therapeutic applications.

Wadhwa et al investigated fusidic acid-loaded liposomes for treating plaque psoriasis.[139] Formulations exhibited varying physicochemical properties, with sizes ranging from 572.7 to 740.1 nm and entrapment efficiencies between 52.1% and 72.6%. These stable liposomes demonstrated enhanced anti-psoriatic efficacy compared to conventional treatments in a mouse tail model. The study highlights the potential of liposomes as effective drug delivery systems for skin disorders.

Lipospheres

Lipospheres are nanoparticles comprising a hydrophobic core enveloped by a phospholipid coating. These particles offer advantages over other lipid-based nanoparticles, including low cost, enhanced stability, simple production, controlled release, and excellent water dispersibility.[140] Demonstrating versatility, lipospheres have been effectively administered via oral, intravenous, and transdermal routes for treating various diseases, including psoriasis.

Chen et al evaluated curcumin-loaded liposphere gel for psoriasis treatment, comparing its efficacy to a solution formulation.[141] Produced lipospheres, averaging 47 nm, were incorporated into a gel base. Enhanced drug permeation through skin layers was observed in a mouse model. The liposphere gel demonstrated superior therapeutic efficacy and histopathological improvement compared to the solution, accompanied by reduced TNF-α, IL-22, and IL-17 levels. These results emphasize the promise of lipospheres as an effective strategy for treating psoriasis.

Ethosomes

Ethosomes, ethanol-based phospholipid vesicles, excel in topical drug delivery due to their flexibility and softness. Their high ethanol content disrupts both ethosomal and stratum corneum lipid bilayers, enhancing skin penetration. This fluidization allows ethosomes to traverse the modified skin barrier and release their contents into deeper layers.

Zhang et al developed psoralen-loaded ethosomes with particle sizes varying from 56.71 to 159.07 nm, achieving optimal encapsulation efficiency at approximately 150 nm.[143] Compared to ethanolic psoralen tincture, ethosomes demonstrated a sevenfold increase in drug deposition within rat skin. This enhanced permeation and penetration suggest reduced toxicity and improved therapeutic efficacy for long-term skin disorder management, including psoriasis.

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are composed of physiological lipids and surfactants. Drug incorporation occurs either within the lipid matrix or as a surrounding layer.[144] Solid lipid nanoparticles (SLNs) provide benefits including regulated drug release, decreased skin irritation, and enhanced protection for the drug when compared to other topical delivery systems. Their size facilitates enhanced drug permeation through close contact with the stratum corneum.[145,146] These characteristics make SLNs promising candidates for topical psoriasis treatments.[147]

Pradhan et al investigated SLNs as a sustained-release delivery system for fluocinolone acetonide.[148] Optimized SLNs, characterized by 107.4 nm particle size, 87% entrapment efficiency, 2% lipid, 1% surfactant, and 0.06% drug concentrations, exhibited controlled drug release following Higuchi kinetics. In contrast, the drug suspension displayed rapid zero-order release in vitro. SLNs demonstrated enhanced fluocinolone acetonide delivery to the epidermis compared to the suspension.[149] These findings highlight the potential of SLNs for developing innovative psoriasis treatments.

Nanostructured Lipid Carriers

Nanostructured lipid carriers (NLCs) offer advantages over traditional formulations. NLCs enhance drug loading, control release, biocompatibility, and bioavailability, enabling diverse administration routes.[150] Their superior penetration ability makes NLCs promising candidates for topical drug delivery systems.

Nanoemulsions of lipids (NLCs) demonstrate occlusive qualities that minimize transepidermal water loss and improve skin hydration by creating a lipid monolayer. These features, combined with their ability to deliver drugs effectively, have sparked interest in utilizing NLCs for treating skin conditions such as psoriasis.[151]

Avasatthi et al formulated a methotrexate-loaded nanostructured lipid carrier (NLC) nanogel.[152] Optimized using Precirol ATO 5, the NLC exhibited a 278 nm particle size, 0.231 polydispersity index, and 22.3% entrapment efficiency. In vitro and in vivo studies demonstrated enhanced PASI scores and prolonged drug circulation following 48-hour application compared to controls. These findings underscore the potential of NLCs for developing novel psoriasis treatments.

Microneedles

Microneedles represent an innovative system for delivering drugs intradermally, consisting of a patch with vertical microneedles that penetrate the stratum corneum. Constructed from various materials, microneedles require sufficient

strength and toughness for effective function.[153] With lengths ranging from 25 to 2000 microns, microneedles penetrate the stratum corneum without activating pain receptors.

Microneedles enhance drug bioavailability by creating microchannels through the skin. This bypasses the initial skin barriers, facilitating drug deposition in the stratum corneum and improving permeability.[154] Diverse microneedle types, varying in mechanism and material, have been developed to optimize this delivery system.

Microneedles are categorized into four types: solid, coated, dissolving, and hollow. While all types have potential applications, only dissolving microneedles have been studied for psoriasis treatment.[155] Dissolving microneedles (DMNs) are biodegradable, dissolving upon skin insertion.[155] The drug is incorporated into the polymer matrix. Material selection is crucial, requiring sufficient strength for skin penetration and subsequent biodegradation without toxicity. Given the body's exposure to needle materials, biodegradability and metabolizability are essential.[156] DMNs offer controlled drug release through material selection.

Tekko et al combined nanotechnology and microneedles by developing methotrexate disodium-loaded nanocrystal patches.[157] After optimizing and characterizing the patches, in vitro release studies were conducted. Subsequent in vivo studies in Sprague Dawley rats compared the microneedle patch with oral methotrexate administration.[158] The patch demonstrated sustained methotrexate release over 72 hours, attributed to skin retention. These findings support further investigation of microneedle-based methotrexate delivery in psoriasis models.[159]

Limited studies have explored microneedle-based drug delivery for psoriasis.[160] Patients reported positive experiences, and PASI scores decreased. While these results demonstrate potential, larger studies with control groups are needed to confirm the findings.

Future Prospects

Translational medicine has revolutionized psoriasis care, but significant challenges persist. While genetics undeniably influence disease expression, the mechanisms underlying environmental triggers remain elusive. The microbiome, stress, and infections, including the lessons from COVID-19, likely play critical roles.[161] A systems medicine approach, incorporating preventive, predictive, personalized, and participatory principles, aims to prevent severe disease and comorbidities.[162] This involves stratifying patients based on integrated omics data to optimize treatment selection and dosage. Early intervention, initiated promptly after diagnosis, facilitates multimorbidity screening, patient education, and timely therapeutic initiation.[163] Such strategies may modify disease course by preventing tissue-resident memory T cell accumulation. IL-17 and IL-23 remain central therapeutic targets, but identifying additional cytokines and intracellular signaling pathways is essential. The systemic inflammatory nature of psoriasis, including adipose inflammation, demands further exploration, especially regarding biologics' potential in cardiovascular disease prevention.[164]

Psoriasis taxonomy is evolving as molecular and genomic insights refine clinical phenotypes. While high-income countries primarily drive treatment paradigms, psoriasis is a global burden.[165] The Global Psoriasis Atlas, collaborating with WHO, International Psoriasis Council, International League of Dermatological Societies, and International Federation of Psoriasis Associations, is crucial for understanding global epidemiology and economic impact.[166] Its goal of ensuring worldwide access to optimal psoriasis care is essential. Introducing low-cost biosimilars in low-income countries requires careful benefit-risk assessment.[167] Topical therapies, though foundational, necessitate improvements in efficacy, durability, and aesthetics. Biologics and novel small molecules have transformed severe psoriasis management, but long-term registries are needed to assess real-world risk-benefit profiles. Identifying factors differentiating those with transient guttate psoriasis from those developing chronic plaque disease is crucial for future therapeutic strategies.[168–170] This requires prospective analysis of immunological, genetic, and environmental factors.

Conclusions

While conventional oral and topical therapies have long been the cornerstone of psoriasis treatment, the advent of biologic therapies has fundamentally transformed the management of this chronic, inflammatory skin condition. Psoriasis, characterized by rapid skin cell turnover and the formation of thick, scaly plaques, has historically been managed through topical corticosteroids, vitamin D analogs, and oral systemic agents such as methotrexate and cyclosporine.[171] While these therapies are effective for many patients, they are often limited by side effects, long-term

use complications, and varying patient responses. The introduction of biologic therapies, which target specific immune system pathways involved in the disease's pathophysiology, such as the interleukin-17 (IL-17), interleukin-23 (IL-23), and tumor necrosis factor (TNF) pathways, has provided a more precise and effective treatment option. These biologics offer dramatic improvements in patient outcomes, achieving better clearance of plaques, reducing inflammation, and improving quality of life.[172]

However, despite the substantial benefits biologics provide, challenges persist. One of the primary concerns is treatment failure, which can occur in two forms: primary failure, where the patient does not respond adequately to the biologic treatment, and secondary failure, where the patient initially responds but loses efficacy over time.[173] These challenges highlight the complexity of psoriasis treatment and emphasize the need for continuous innovation in therapeutic approaches. Treatment resistance may arise due to a variety of factors, including patient-specific genetic and immunological differences, variations in drug absorption, and the development of neutralizing antibodies against biologic agents.[174] Therefore, there is a critical need to explore alternative strategies that can address these issues and further optimize treatment outcomes.

In response to these challenges, researchers are focusing on developing novel drug delivery systems that enhance the effectiveness and precision of treatments. One promising avenue is the use of nanoparticles for targeted drug delivery. Nanoparticles, which are typically between 1 and 100 nanometers in size, offer several advantages over traditional drug delivery methods.[175] By encapsulating therapeutic agents, nanoparticles can be designed to overcome the skin's natural barrier, which is one of the primary obstacles in treating psoriasis topically. These particles can be engineered to target specific cells or tissues involved in the inflammatory process, allowing for localized drug delivery directly to the affected skin areas.[176] This approach not only improves drug efficacy but also reduces the likelihood of systemic side effects. Moreover, lipid-based nanoparticles—which use lipid molecules as the carrier system—are gaining significant attention in dermatology due to their biocompatibility, ability to encapsulate poorly water-soluble drugs, and potential for sustained drug release.[177] The lipid-based structure of these nanoparticles mimics the skin's natural lipid layers, aiding in penetration through the skin's barrier and ensuring that the therapeutic agents are delivered directly to the site of inflammation with minimal waste.

Another exciting development in psoriasis treatment is the microneedle technology, which offers a minimally invasive approach to drug delivery. Microneedles are tiny, needle-like structures, typically ranging from 25 to 100 micrometers in length, that can painlessly penetrate the skin's outermost layer, the stratum corneum, to deliver drugs directly into the deeper layers of the skin. This innovative technology overcomes the limitations of conventional topical treatments that often struggle to reach the deeper layers of the skin where psoriasis lesions are located. Microneedles can be used to administer both biologic therapies and small molecules directly to the target site, offering precise control over the dosage and timing of drug release. This method has the potential to increase drug absorption, improve therapeutic efficacy, and significantly reduce the risk of systemic side effects. While dissolving microneedles—which dissolve upon insertion into the skin—have shown promising results in clinical trials, further research is necessary to evaluate the full potential of different microneedle designs, materials, and formulations. For instance, multi-layered or coated microneedles may allow for controlled and sustained release of drugs over an extended period, enhancing the therapeutic effect and reducing the need for frequent treatments.[178]

In conclusion, the combination of advanced biologic therapies with cutting-edge drug delivery systems, such as nanoparticles and microneedles, represents a promising future for the treatment of psoriasis. These novel approaches aim to address the limitations of conventional therapies, such as the risk of treatment failure and side effects, by improving the precision and effectiveness of drug delivery. As research in these areas continues to evolve, these innovative strategies could offer more effective, personalized, and tolerable treatment options for psoriasis patients. By overcoming the barriers associated with traditional treatments and optimizing drug delivery systems, these advancements have the potential to significantly improve patient outcomes and quality of life, offering new hope for individuals struggling with this chronic skin condition.

Data Sharing Statement

No data was used for the research described in the article.

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Author Contributions

SG and JL designed and conceptualized the report. MM wrote the first draft of the manuscript. JY and YS reviewed and revised the manuscript. All authors have read and approved the article. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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