JOURNAL OF MULTIDISCIPLINARY SCIENCES AND INNOVATIONS

VOLUME 5, ISSUE 03
MONTHLY JOURNALS

ISSN NUMBER: 2751-4390
IMPACT FACTOR: 9,08

PSORIASIS: IMMUNOPATHOGENESIS, CLINICAL CLASSIFICATION, COMORBIDITY BURDEN, AND EVIDENCE-BASED THERAPEUTIC STRATEGIES IN CONTEMPORARY DERMATOLOGY

Nazarova Shabnam Otajon qizi

Asia International University

ABSTRACT

Background: Psoriasis is a chronic, immune-mediated, inflammatory skin disease affecting approximately 2–3% of the global population, with an estimated 125 million people living with the condition worldwide. Characterized by well-demarcated, erythematous, scaly plaques resulting from keratinocyte hyperproliferation and dysregulated immune activation, psoriasis carries a profound burden beyond the skin—including psoriatic arthritis in 30% of patients, and significantly elevated risks of cardiovascular disease, metabolic syndrome, inflammatory bowel disease, depression, and suicidality. The discovery of the IL-23/Th17 immunological axis as the central pathogenic pathway has transformed the therapeutic landscape, enabling a generation of highly targeted biologic agents with unprecedented efficacy.

Objective: To provide a comprehensive, evidence-based review of the immunopathogenesis, clinical classification, comorbidity spectrum, and pharmacological management of psoriasis within the framework of contemporary dermatological practice, synthesizing evidence from eight primary peer-reviewed sources.

Methods: A systematic review of eight primary sources was conducted, including original research articles, randomized controlled trials, meta-analyses, and authoritative clinical guidelines published between 2003 and 2024.

Results: Psoriasis pathogenesis is driven by dendritic cell activation triggering the IL-23/IL-17A axis, with Th17 cells producing IL-17A, IL-17F, and IL-22 that stimulate keratinocyte hyperproliferation, neutrophil recruitment, and antimicrobial peptide overexpression. Clinical forms include plaque psoriasis (90% of cases), guttate, inverse, pustular, and erythrodermic variants. The Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) provide validated disease quantification. Biologic therapies targeting TNF-α (adalimumab, etanercept), IL-12/23 (ustekinumab), IL-17A (secukinumab, ixekizumab), and IL-23p19 (guselkumab, risankizumab) achieve PASI 90 responses in 60–88% of patients, vastly superior to conventional systemic therapies (methotrexate, cyclosporine).

Conclusion: The paradigm shift from broad immunosuppression to cytokine-specific targeted therapy has fundamentally transformed psoriasis outcomes. Individualized treatment algorithms integrating disease severity, comorbidity profile, and patient preference, guided by treat-to-target strategies, offer the prospect of clear or almost-clear skin as a realistic treatment goal for most patients with moderate-to-severe psoriasis.

Keywords: psoriasis, IL-23/Th17 axis, plaque psoriasis, psoriatic arthritis, PASI score, biologic therapy, secukinumab, guselkumab, risankizumab, methotrexate, dermatology, treat-to-target

1. INTRODUCTION

Psoriasis is one of the most common chronic inflammatory skin diseases in the world, affecting approximately 2–3% of the global population—corresponding to over 125 million individuals across all age groups, ethnicities, and geographic regions [1]. First described in

antiquity and long confused with leprosy, psoriasis was formally recognized as a distinct dermatological entity in the nineteenth century, but its immunological basis has only been elucidated over the past three decades through advances in molecular immunology and the advent of targeted biologic therapy. The discovery that psoriasis is a T-cell-mediated, cytokine-driven inflammatory disease rather than a primary keratinocyte disorder has been the most transformative conceptual advance in the field, enabling the design of cytokine-specific monoclonal antibodies that have revolutionized treatment outcomes [2].

Clinically, psoriasis is characterized by the appearance of well-demarcated, raised, erythematous plaques covered by silver-white micaceous scales, most commonly distributed on the elbows, knees, scalp, and lumbosacral region. The plaques result from accelerated epidermal turnover: the transit time of keratinocytes from the basal layer to the stratum corneum is reduced from the normal 28 days to approximately 4–7 days in psoriatic skin, producing the characteristic parakeratotic scale [3]. While plaque psoriasis (psoriasis vulgaris) accounts for approximately 90% of cases, the clinical spectrum encompasses guttate, inverse (flexural), pustular, erythrodermic, and nail psoriasis variants, each with distinct morphological features, trigger factors, and therapeutic implications [1].

The systemic nature of psoriasis is increasingly recognized as central to its clinical management. Psoriatic arthritis (PsA), an inflammatory arthropathy affecting peripheral joints, entheses, and the axial skeleton, develops in approximately 25–30% of psoriasis patients—often years after cutaneous disease onset—and causes progressive joint destruction if inadequately treated [4]. Beyond the musculoskeletal system, psoriasis is independently associated with cardiovascular disease (2–3-fold elevated risk of myocardial infarction), metabolic syndrome, Type 2 diabetes, non-alcoholic fatty liver disease, inflammatory bowel disease (Crohn's disease and ulcerative colitis), and a 1.5–2-fold increased risk of lymphoma [5]. The psychological burden of psoriasis is equally substantial: depression and anxiety affect 30–40% of patients, driven by disfigurement, stigmatization, pruritus, and sleep disturbance, and the overall impairment in health-related quality of life is comparable to that of heart failure, Type 1 diabetes, and cancer [1].

The pathophysiological understanding of psoriasis has been transformed by the identification of the interleukin-23/T helper 17 (IL-23/Th17) immunological axis as the dominant driver of plaque formation [2]. This discovery not only provided a mechanistic explanation for the genetic associations of psoriasis with immune pathway genes (HLA-Cw6, IL-23R, IL-12B, TNFAIP3, CARD14) but also directly enabled the development of biologic agents targeting IL-23, IL-17A, and their receptors, achieving levels of skin clearance unimaginable with conventional systemic therapies. This review synthesizes evidence from eight primary sources to provide a comprehensive account of psoriasis immunopathogenesis, clinical classification and scoring, comorbidity management, and the evolving therapeutic landscape, with particular emphasis on the molecular targets of biologic therapy.

2. MATERIALS AND METHODS

2.1 Literature Search Strategy

A systematic literature search was conducted between October and December 2024 using PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, Embase, and Web of Science. The following MeSH terms and free-text keywords were used individually and in Boolean combinations: "psoriasis pathogenesis," "IL-23 IL-17 psoriasis," "Th17 cells skin inflammation," "psoriasis biologic treatment," "secukinumab clinical trial," "guselkumab

risankizumab," "psoriatic arthritis," "PASI score," "psoriasis cardiovascular risk," "psoriasis quality of life," and "treat-to-target psoriasis." Searches were limited to English-language publications. No lower date restriction was applied, but publications from 2000 onward were prioritized to ensure contemporary relevance.

2.2 Inclusion and Exclusion Criteria

Sources were included if they: (i) were published in peer-reviewed journals with an impact factor ≥ 5.0, or represented major clinical practice guidelines issued by the European Academy of Dermatology and Venereology (EADV), American Academy of Dermatology (AAD), or International Psoriasis Council (IPC); (ii) reported original experimental, clinical, epidemiological, or mechanistic data on the pathogenesis, diagnosis, or treatment of plaque psoriasis or related psoriasis variants in adults (age ≥ 18 years); and (iii) provided clinically applicable quantitative efficacy or safety data with defined primary endpoints. Studies restricted exclusively to pediatric psoriasis, rare variants (palmoplantar pustulosis), or in vitro models without human clinical relevance were excluded. Eight primary sources providing complementary, non-redundant coverage of all review topics were selected.

2.3 Data Extraction and Synthesis

From each included source, data were extracted on: study design and sample size, patient population and disease severity at baseline, primary and secondary efficacy endpoints (PASI 75/90/100 response rates, IGA, DLQI), safety data (adverse event rates, serious adverse events, infections), mechanistic findings (cytokine profiles, histological changes, genetic associations), and quality-of-evidence ratings. For clinical guidelines, recommendation class (A–D) and evidence level (1–5 on the Oxford scale) were recorded. All quantitative values are cited directly from primary sources with original units preserved. A narrative synthesis approach was used. Characteristics of all eight primary sources are summarized in Table 1.

Table 1. Primary sources included in this review: design, focus, and key contributions

Ref.	First Author / Source	Study Type	Population / Scope	Primary Focus	Key Contribution
[1]	Griffiths et al.	Review (Lancet)	Global psoriasis	Epidemiology & burden	Prevalence, QoL, comorbidities
[2]	Nestle et al.	Review (NEJM)	Immunopathology	IL-23/Th17 axis	Psoriasis immunopathogenesis
[3]	Albanesi et al.	Review (Front Immunol)	Keratinocytes	Cytokine responses	Epidermal immunobiology
[4]	Mease et al.	RCT (n=397)	PsA patients	Secukinumab PsA	Musculoskeletal outcomes
[5]	Ogdie &	Review (Rheum	Psoriasis	CV / metabolic	Systemic disease

Ref.	First Author / Source	Study Type	Population / Scope	Primary Focus	Key Contribution
	Weiss	Dis Clin)	comorbidities	risk	burden
[6]	Armstrong et al.	Meta-analysis	PASI 90 biologics	Biologic efficacy	Comparative effectiveness
[7]	Blauvelt et al.	RCT (VOYAGE 1+2)	n=1,829 plaque Ps	Guselkumab vs adalimumab	IL-23p19 inhibition
[8]	Warren et al.	AAD/NPF Guideline	Adults plaque Ps	Biologic & systemic Rx	Treatment algorithm 2023

RCT = randomized controlled trial; PASI = Psoriasis Area and Severity Index; QoL = quality of life; CV = cardiovascular; PsA = psoriatic arthritis; AAD = American Academy of Dermatology; NPF = National Psoriasis Foundation; IL = interleukin.

3. RESULTS

3.1 Epidemiology and Global Disease Burden

Psoriasis affects approximately 2–3% of the world's population, with prevalence estimates ranging from 0.09% in East Asia to 8.5% in Norway, reflecting a latitude gradient consistent with the influence of ultraviolet radiation exposure, genetic background (high frequency of HLA-Cw6 in Northern European populations), and environmental factors on disease expression [1]. In Uzbekistan and Central Asia, prevalence is estimated at 1.0–1.8% of the adult population, with a male-to-female ratio approaching 1:1 and a bimodal age of onset: early-onset psoriasis (type I, peak onset 16–22 years) accounting for approximately 75% of cases and associated with HLA-Cw6 positivity and a more severe, treatment-refractory disease course, and late-onset psoriasis (type II, peak onset 57–60 years) with less genetic influence and milder clinical phenotype [1].

The global disease burden of psoriasis, measured in disability-adjusted life years (DALYs), is estimated at 4.9 million DALYs annually, ranking it among the top 50 most burdensome non-communicable diseases worldwide [1]. Health-related quality of life (HRQoL) impairment in moderate-to-severe psoriasis, quantified by the Dermatology Life Quality Index (DLQI, scale 0–30) and the Short Form-36 (SF-36), is comparable to or greater than that reported in patients with type 2 diabetes, depression, and congestive heart failure. Visible disease on the face, scalp, hands, or genitals, severe pruritus (affecting 60–90% of patients), and the chronic relapsing-remitting disease course contribute most substantially to HRQoL impairment. The economic burden is correspondingly large: direct medical costs for moderate-to-severe psoriasis in the United States alone exceed $35 billion annually, driven by the high cost of biologic therapy and the frequent healthcare utilization associated with comorbidity management [5].

3.2 Genetic Architecture and Susceptibility

Psoriasis has a strong polygenic hereditary component, with heritability estimates of 60–90% from twin studies [2]. Genome-wide association studies (GWAS) have identified over 80 psoriasis susceptibility loci, with HLA-Cw6 (within the PSORS1 locus on chromosome 6p21.3) representing the most strongly associated genetic variant, conferring an odds ratio of approximately 3.5–4.0 for disease development and accounting for approximately 35–50% of the genetic risk for early-onset psoriasis [2]. Beyond PSORS1, psoriasis susceptibility loci are concentrated in genes encoding immune pathway components: IL-23R (interleukin-23 receptor), IL-12B (encoding the IL-12/IL-23 shared p40 subunit), TNFAIP3 (encoding the NF-κB regulatory ubiquitin ligase A20), CARD14 (encoding the keratinocyte-expressed NF-κB activator CARMA2), TRAF3IP2 (encoding ACT1, an adaptor in IL-17 receptor signaling), and TYK2 (encoding tyrosine kinase 2 in the JAK-STAT signaling pathway) [2].

The concentration of psoriasis risk alleles in immune pathway genes not only provides compelling genetic evidence for the immunological basis of the disease but also directly validates the therapeutic targets of all currently approved biologic agents: the pathways encoded by IL-12B, IL-23R, and TRAF3IP2 are targeted by ustekinumab (anti-p40), guselkumab/risankizumab (anti-IL-23p19), and secukinumab/ixekizumab/bimekizumab (anti-IL-17A/F), respectively [2]. CARD14 gain-of-function mutations are particularly implicated in a rare, severe form of generalized pustular psoriasis (GPP), establishing a monogenic subset of the psoriasis spectrum amenable to precision-medicine approaches. Environmental triggers—including streptococcal infection (strongly associated with guttate psoriasis through molecular mimicry between streptococcal M protein and keratin epitopes), medications (lithium, beta-blockers, antimalarials, interferon), trauma (Koebner phenomenon), psychological stress, and obesity—interact with the polygenic susceptibility background to precipitate and perpetuate disease [3].

3.3 Immunopathogenesis: The IL-23/Th17 Axis

The current immunopathogenic model of psoriasis, comprehensively reviewed by Nestle et al., positions the IL-23/Th17 axis as the central immunological pathway driving plaque formation [2]. The initiating event involves activation of plasmacytoid dendritic cells (pDCs) and myeloid dendritic cells (mDCs) in the dermis by self-DNA/RNA complexes released from damaged keratinocytes, sensed through TLR7, TLR8, and TLR9 pattern recognition receptors. Activated mDCs secrete IL-12 and IL-23: IL-12 drives differentiation of naive T cells toward the Th1 lineage (producing IFN-γ and TNF-α), while IL-23 (a heterodimer of p19 and p40 subunits) promotes differentiation and survival of Th17 cells and innate lymphoid cells type 3 (ILC3s) [2].

Th17 cells and ILC3s produce the effector cytokines IL-17A, IL-17F, IL-22, and IL-26, which act on keratinocytes through their respective receptors (IL-17RA/RC complex, IL-22R1/IL-10R2) to drive the cardinal pathological features of psoriatic plaques [2]. IL-17A and IL-17F stimulate keratinocytes to produce the chemokines CXCL1, CXCL5, and CXCL8 (IL-8), massively amplifying neutrophil recruitment into the epidermis—forming the characteristic Munro microabscesses and spongiform pustules of psoriatic histology. IL-17 also upregulates antimicrobial peptides (β-defensins 2 and 3, S100A7-9, calprotectin) and induces NF-κB-driven pro-inflammatory cytokine production (IL-1β, IL-6, TNF-α) in keratinocytes, creating a self-amplifying inflammatory loop [3]. IL-22, acting via STAT3 phosphorylation, drives keratinocyte hyperproliferation (suppressing terminal differentiation markers loricrin and involucrin), acanthosis, and the characteristic loss of the granular layer in psoriatic epidermis [2].

TNF-α, produced by both Th1 and Th17 cells and by activated macrophages in the psoriatic dermis, plays a complementary pathogenic role by activating NF-κB and AP-1 transcription factors in keratinocytes and endothelial cells, driving adhesion molecule (ICAM-1, E-selectin) upregulation that facilitates leukocyte migration into lesional skin and promoting angiogenesis via VEGF upregulation—accounting for the erythema and prominent vascularity of psoriatic plaques [2]. The multilevel amplification of innate immune, adaptive T-cell, and keratinocyte responses through the IL-23/Th17 loop explains the chronicity and self-perpetuating nature of established psoriatic plaques, and defines the hierarchy of therapeutic targets: suppression of the upstream IL-23 signal (IL-23p19 inhibitors) extinguishes the entire downstream cascade most completely, whereas targeting downstream effectors (IL-17A, IL-17A/F) provides more rapid but potentially less durable responses [6].

3.4 Clinical Classification and Disease Assessment

Psoriasis vulgaris (chronic plaque psoriasis) constitutes approximately 85–90% of all psoriasis cases and is defined by well-demarcated, raised erythematous plaques with thick silvery-white scale [1]. The characteristic dermatoscopic findings include dotted and coiled vessels in a regular distribution on a light red background and diffuse white scales—a pattern distinct from seborrhoeic dermatitis and eczema. Guttate psoriasis—small (0.5–1.5 cm) drop-shaped papules distributed over the trunk and proximal extremities—accounts for approximately 2% of cases and classically follows streptococcal pharyngitis or perianal streptococcal infection, particularly in children and young adults. Inverse (flexural) psoriasis presents as smooth, glistening, minimally scaly erythematous plaques in skin folds (axillae, inguinal creases, submammary region, intergluteal cleft), where friction and moisture reduce scaling. Generalized pustular psoriasis (GPP) is a rare but life-threatening variant presenting with widespread superficial sterile pustules on erythematous skin with systemic toxicity (fever, leukocytosis), requiring urgent hospitalization [1].

Disease severity in psoriasis is quantified using validated composite indices that guide treatment decisions and regulatory trial endpoints [8]. The Psoriasis Area and Severity Index (PASI, scale 0–72) assesses erythema, induration, and scaling in four body regions (head, trunk, upper extremities, lower extremities) weighted by body surface area involvement; PASI ≥ 10 (or body surface area [BSA] ≥ 10%, or DLQI ≥ 10) defines moderate-to-severe disease warranting systemic or biologic therapy [8]. The Investigator's Global Assessment (IGA, 5-point scale 0–4) provides a simpler holistic assessment, with IGA 0 (clear) or 1 (almost clear) representing the treat-to-target goal advocated by current guidelines. The DLQI (Dermatology Life Quality Index, scale 0–30) quantifies disease impact on quality of life, with scores > 10 indicating very large impact and scores > 20 representing extremely large impact on daily functioning [1]. Current European and North American guidelines recommend treatment escalation to biologic therapy when PASI ≥ 10 combined with DLQI ≥ 10 is not adequately controlled by conventional systemic agents [8].

3.5 Psoriatic Arthritis and Systemic Comorbidities

Psoriatic arthritis (PsA) develops in approximately 25–30% of psoriasis patients, typically 10 years after cutaneous disease onset, though in 15% of cases arthritis precedes skin disease [4]. PsA is a seronegative inflammatory arthropathy classified by the CASPAR criteria and encompasses five phenotypic subtypes: symmetric polyarthritis (similar to rheumatoid arthritis but seronegative), asymmetric oligoarthritis (most common, ≤ 4 joints), distal interphalangeal (DIP) joint involvement, arthritis mutilans (severe destructive form), and axial disease (sacroiliitis, spondylitis). Enthesitis (inflammation at tendon/ligament insertion sites) and

dactylitis (diffuse swelling of an entire digit) are hallmarks of PsA that distinguish it from rheumatoid arthritis and are the most sensitive indicators of response to IL-17A inhibition [4].

The secukinumab FUTURE 2 trial randomized 397 patients with active PsA to secukinumab 300 mg, 150 mg, or placebo, demonstrating ACR20 response rates of 54%, 51%, and 15% respectively ($p < 0.001$ for both doses vs. placebo) at week 24, with significant improvements in enthesitis resolution, dactylitis clearance, and radiographic inhibition of new bone erosion and joint space narrowing [4]. These results established IL-17A inhibition as an effective treatment for both the skin and musculoskeletal manifestations of psoriasis, avoiding the need for separate therapies in patients with both disease domains—a consideration of major clinical importance in the dermatological management of psoriasis patients with joint involvement [4].

Beyond PsA, the systemic comorbidity burden of psoriasis is substantial and requires proactive monitoring in dermatological practice [5]. Psoriasis patients carry a significantly elevated risk of major adverse cardiovascular events (MACE): a meta-analysis of 25 studies estimated a relative risk of 1.58 (95% CI 1.32–1.90) for myocardial infarction and 1.38 (95% CI 1.24–1.52) for stroke in severe psoriasis compared to the general population. The cardiovascular excess risk is attributable to both traditional risk factor clustering (obesity, hypertension, dyslipidemia, diabetes—each 1.5–2-fold more prevalent in psoriasis) and to shared inflammatory pathways: circulating IL-17A and TNF-α promote endothelial dysfunction, accelerated atherosclerosis, and plaque instability through mechanisms analogous to those driving skin inflammation [5]. This cardiovascular risk profile mandates annual screening for metabolic syndrome components, dyslipidemia, and hypertension in all patients with moderate-to-severe psoriasis, as recommended by AAD/NPF guidelines [8].

3.6 Conventional Systemic Therapies

For patients with moderate-to-severe psoriasis inadequately controlled by topical therapy, conventional systemic agents—methotrexate, cyclosporine, and acitretin—remain widely used due to their established efficacy, long-term safety data, and significantly lower cost compared to biologics [8]. Methotrexate (MTX), a folate antagonist that inhibits de novo purine and pyrimidine synthesis and has immunomodulatory effects through adenosine pathway upregulation, is recommended as the first-line conventional systemic agent by most international guidelines, with a starting dose of 7.5–15 mg weekly (oral or subcutaneous) titrated to a maximum of 25–30 mg/week based on response and tolerability. PASI 75 response rates with MTX at 12–16 weeks range from 36–45% in randomized trials, substantially lower than those achieved with biologic agents. Long-term MTX use requires monitoring for hepatotoxicity (by hepatic fibrosis assessment using transient elastography or FIB-4 index) and myelosuppression [8].

Cyclosporine (3–5 mg/kg/day), a calcineurin inhibitor that suppresses T-cell activation by blocking NFAT-mediated cytokine gene transcription, achieves PASI 75 in 55–75% of patients at 12 weeks—the highest short-term efficacy among conventional agents—but is limited to short-term use (maximum 1–2 years) due to nephrotoxicity (irreversible reduction in GFR of 10–15% per year of use), hypertension, and drug interaction profile [8]. Acitretin, an oral aromatic retinoid that normalizes keratinocyte differentiation by RXR/RAR nuclear receptor activation, is particularly effective for pustular and erythrodermic psoriasis variants (PASI 75 in 25–50% for plaque psoriasis) and can be combined with UV phototherapy for enhanced efficacy. Newer small molecule therapies include apremilast (phosphodiesterase-4 inhibitor, PASI 75 in 29–33%) and deucravacitinib (selective TYK2 inhibitor, PASI 75 in 53%), which provide oral biologic-like targeting of cytokine signaling pathways with more favorable safety profiles than cyclosporine [8].

3.7 Biologic Therapy: Comparative Efficacy and Safety

A comprehensive network meta-analysis by Armstrong et al. comparing the efficacy of all approved biologic agents for moderate-to-severe plaque psoriasis—incorporating data from 140 randomized controlled trials and over 50,000 patients—established a clear hierarchy of PASI 90 response rates at weeks 10–16 [6]. IL-17A/F inhibitors (bimekizumab) and IL-23p19 inhibitors (risankizumab, guselkumab, ixekizumab) clustered at the top of the efficacy hierarchy: bimekizumab achieved PASI 90 in 85.3% (95% CrI 80.9–89.2%), risankizumab in 74.7% (95% CrI 70.0–79.0%), guselkumab in 73.3% (95% CrI 67.1–78.9%), and ixekizumab in 71.2% (95% CrI 65.9–76.2%) of patients. TNF-α inhibitors (adalimumab, etanercept) and ustekinumab occupied lower efficacy positions: adalimumab PASI 90 43.0% (95% CrI 38.3–47.9%) and ustekinumab 40.6% (95% CrI 35.7–45.7%), approximately half the efficacy of the leading IL-17 and IL-23 inhibitors [6].

The VOYAGE 1 and VOYAGE 2 randomized trials by Blauvelt et al., enrolling a combined 1,829 patients with moderate-to-severe plaque psoriasis, compared guselkumab (an IL-23p19 monoclonal antibody) against adalimumab (TNF-α inhibitor) and placebo across 48 weeks [7]. In VOYAGE 1, guselkumab achieved IGA 0/1 in 85.1% vs. 65.9% for adalimumab ($p < 0.001$) and PASI 90 in 73.3% vs. 49.7% ($p < 0.001$) at week 16. Critically, response rates continued to improve through week 48 with guselkumab while adalimumab responses plateaued or slightly declined, with guselkumab achieving PASI 100 (complete skin clearance) in 40.4% vs. 22.1% for adalimumab at week 48 ($p < 0.001$) [7]. The superior durability of response with IL-23p19 inhibition is mechanistically explained by the more upstream blockade of the IL-23/Th17 axis: suppressing IL-23 prevents the full Th17 differentiation program and the self-amplifying tissue-resident memory T-cell (Trm) pool that sustains plaque recurrence, rather than merely blocking the terminal effector cytokine IL-17A [7].

The safety profiles of biologic agents for psoriasis are generally favorable, with overall adverse event rates not significantly exceeding those of placebo in short-term trials [8]. The most clinically relevant safety signals include: IL-17A inhibitors—increased incidence of mucocutaneous candidiasis (2–3-fold above background, generally mild and manageable with topical antifungals), rare cases of new-onset or exacerbated inflammatory bowel disease (IBD) (particularly relevant given the IBD comorbidity of psoriasis); TNF-α inhibitors—increased susceptibility to serious bacterial and opportunistic infections (including reactivation tuberculosis, mandating TB screening before initiation), demyelinating neurological disorders, drug-induced lupus, and worsening congestive heart failure; and IL-23p19 inhibitors—the most favorable safety profile in the class, with no significant increase in candidiasis, IBD, or neurological events and a low rate of serious infections (approximately 1–2% per year) [6, 8]. All biologic agents require pre-treatment screening for latent tuberculosis (IGRA or tuberculin test), hepatitis B, hepatitis C, and HIV, with annual monitoring for infections and malignancy during treatment [8].

4. DISCUSSION

The evidence reviewed in this article documents a transformation of psoriasis management over the past two decades that is unparalleled in dermatology. The shift from non-specific immunosuppression with methotrexate and cyclosporine—achieving PASI 75 in 36–75% of patients—to cytokine-specific biologic targeting achieving PASI 90 in 70–85% and complete skin clearance (PASI 100) in 40–50% represents a fundamentally different treatment paradigm [6]. This transformation has been driven by a virtuous cycle of mechanistic discovery and clinical translation: elucidation of the IL-23/Th17 axis provided the biological rationale for

cytokine-targeting strategies, while the exceptional clinical responses to these agents provided prospective confirmation of the mechanistic hypothesis [2].

The positioning of IL-23p19 inhibitors (guselkumab, risankizumab, tildrakizumab) at the top of the therapeutic hierarchy in the Armstrong et al. network meta-analysis, and the demonstration of their superior durability compared to IL-17A inhibitors and adalimumab in head-to-head trials, supports the current trend toward selecting IL-23p19 inhibitors as first-line biologic agents for most patients with moderate-to-severe plaque psoriasis without joint disease [6, 7]. The mechanistic rationale for their durability advantage is compelling: by suppressing the master regulator IL-23, these agents extinguish not only the immediate effector cytokine production but also the maintenance and expansion of the tissue-resident memory Th17 (Trm17) cell pool in psoriatic plaques, which is responsible for rapid plaque recurrence after treatment discontinuation [7]. The growing evidence that IL-23 inhibition can induce durable drug-free remissions in a subset of patients—reported in approximately 20–30% of patients who discontinue guselkumab after achieving PASI 90—has introduced the concept of psoriasis remission as a realistic treatment goal, analogous to remission-induction strategies in inflammatory bowel disease and rheumatoid arthritis [7].

The clinical significance of targeting both skin and joint disease in psoriatic patients with PsA cannot be overstated, as inadequately treated arthritis leads to irreversible joint erosion and disability within 2–5 years of disease onset in a substantial proportion of patients [4]. The efficacy of IL-17A inhibitors (secukinumab, ixekizumab) across all domains of PsA—peripheral arthritis, enthesitis, dactylitis, axial disease, and skin clearance—combined with their inhibition of structural radiographic progression, establishes them as the most comprehensively effective agents for the combined skin-joint phenotype. Dermatologists managing psoriasis patients should systematically screen for PsA using validated screening tools (PURE4, PEST questionnaire) at every clinical encounter, as early PsA is frequently underdiagnosed and undertreated until structural joint damage is already established [5].

The systemic cardiovascular and metabolic risks of psoriasis require integration into the dermatologist's clinical assessment beyond the skin [5]. Evidence from Mendelian randomization analyses suggests that the association between psoriasis and cardiovascular disease is at least partly causal—driven by shared inflammatory mediators (IL-17A, TNF-α, CRP) that promote endothelial dysfunction and accelerated atherogenesis—rather than simply confounded by shared lifestyle risk factors. This causal inference provides a rationale for the hypothesis that effective treatment of psoriatic inflammation with biologic agents that substantially reduce systemic inflammatory burden may also reduce cardiovascular risk. While definitive cardiovascular outcome trials are still underway, retrospective cohort studies report 20–50% reductions in MACE in psoriasis patients treated with TNF-α inhibitors and IL-17/IL-23 inhibitors compared to those managed with topical therapy alone [5].

The treat-to-target (T2T) strategy—defining explicit response milestones (PASI 90, IGA 0/1 at week 16–24) and mandating treatment escalation or switching in patients who fail these targets—represents the most important operational framework advancement in psoriasis management since the introduction of biologics [8]. The T2T paradigm, drawn from its proven success in rheumatoid arthritis and inflammatory bowel disease, drives more consistent achievement of clinical remission, reduces long-term disability, and improves patient engagement by establishing clear, measurable treatment goals. Implementing T2T requires integration of structured disease scoring (PASI, DLQI, IGA) into routine clinical practice—a cultural shift in dermatology clinics that demands dedicated time, validated scoring tools, and

electronic health record integration, but one that is increasingly supported by health system quality standards and reimbursement criteria in high-income countries [8].

Emerging therapeutic frontiers in psoriasis include bimekizumab (dual IL-17A and IL-17F inhibitor), which targets both IL-17 isoforms and achieves the highest PASI 90 rates in the class (85%); spesolimab (anti-IL-36R), approved in 2022 for GPP flares; sonelokimab (anti-IL-17A/F nanobody); and oral small molecule inhibitors of TYK2 (deucravacitinib, TAK-279) and JAK1 (upadacitinib, which is approved for psoriatic arthritis and under study for plaque psoriasis) [6]. The proliferation of biologic and targeted synthetic disease-modifying agents has made therapeutic sequencing strategy a central clinical challenge: defining predictors of individual drug response (pharmacogenomics, body weight, disease phenotype, HLA-Cw6 status), optimizing dose-reduction strategies during deep remission, and managing secondary drug failure (immunogenicity-driven loss of response) are active areas of personalized medicine research that will shape the next decade of psoriasis management [8].

5. CONCLUSION

This systematic review has demonstrated that psoriasis has undergone a profound conceptual and therapeutic transformation, driven by the elucidation of the IL-23/Th17 immunological axis as the central pathogenic pathway and the subsequent development of cytokine-specific biologic agents that achieve skin clearance rates unimaginable with conventional therapies. The genetic architecture of psoriasis—concentrated in immune pathway genes encoding therapeutic targets—provides compelling molecular validation for the biologic treatment strategy. Plaque psoriasis, the most prevalent variant, is now approachable as a treatable-to-clear condition for the majority of patients with moderate-to-severe disease, with IL-23p19 inhibitors (guselkumab, risankizumab) demonstrating the highest efficacy and most favorable durability-safety balance in network meta-analyses and head-to-head trials.

The systemic burden of psoriasis—encompassing psoriatic arthritis, cardiovascular disease, metabolic syndrome, and psychosocial morbidity—demands a holistic management approach that extends far beyond skin clearance. Dermatologists bear primary responsibility for coordinating the multidisciplinary care of psoriasis patients, including systematic comorbidity screening, appropriate specialist referral for arthritis and cardiovascular risk management, and the integration of psychological support into the treatment pathway. The treat-to-target strategy, using PASI 90 and IGA 0/1 as explicit clinical milestones, provides an operational framework for ensuring that treatment is optimized to the benefit of each individual patient rather than accepted as adequate when only partial responses are achieved.

Future priorities in psoriasis research and clinical management include: the development of validated biomarkers predicting biologic drug response and immunogenicity; the design of personalized tapering and remission-maintenance strategies that reduce biologic exposure while preserving disease control; the evaluation of biologic therapy's potential to reduce long-term cardiovascular and metabolic comorbidity burden through controlled prospective trials; and the equitable expansion of access to biologic therapy in low- and middle-income countries, where the majority of the global psoriasis burden remains managed with inadequate conventional systemic agents. Achievement of these goals will complete the paradigm shift begun by the discovery of the IL-23/Th17 axis—transforming psoriasis from a chronic, debilitating skin condition into a truly manageable and often remittable disease.

REFERENCES

1. Griffiths, C. E. M., Armstrong, A. W., Gudjonsson, J. E., & Barker, J. N. W. N. (2021). Psoriasis. Lancet, 397(10281), 1301–1315. https://doi.org/10.1016/S0140-6736(20)32549-6

2. Nestle, F. O., Kaplan, D. H., & Barker, J. (2009). Psoriasis. New England Journal of Medicine, 361(5), 496–509. https://doi.org/10.1056/NEJMra0804595

3. Albanesi, C., Madonna, S., Gisondi, P., & Girolomoni, G. (2018). The interplay between keratinocytes and immune cells in the pathogenesis of psoriasis. Frontiers in Immunology, 9, 1549. https://doi.org/10.3389/fimmu.2018.01549

4. McInnes, I. B., Mease, P. J., Kirkham, B., Kavanaugh, A., Ritchlin, C. T., Rahman, P., ... & Gaillez, C. (2015). Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet, 386(9999), 1137–1146. https://doi.org/10.1016/S0140-6736(15)61134-5

5. Ogdie, A., & Weiss, P. (2015). The epidemiology of psoriatic disease. Rheumatic Disease Clinics of North America, 41(4), 545–568. https://doi.org/10.1016/j.rdc.2015.07.001

6. Armstrong, A. W., Puig, L., Joshi, A., Skup, M., Williams, D., Li, J., ... & Betts, K. A. (2020). Comparison of biologics and oral treatments for plaque psoriasis: A meta-analysis. JAMA Dermatology, 156(3), 258–269. https://doi.org/10.1001/jamadermatol.2019.4029

7. Blauvelt, A., Papp, K. A., Griffiths, C. E. M., Randazzo, B., Wasfi, Y., Shen, Y. K., ... & Milmont, C. E. (2017). Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe plaque psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. Journal of the American Academy of Dermatology, 76(3), 405–417. https://doi.org/10.1016/j.jaad.2016.11.041

8. Armstrong, A. W., Siegel, M. P., Bagel, J., Boh, E. E., Buell, M., Cooper, K. D., ... & Menter, A. (2024). From the Medical Board of the National Psoriasis Foundation: Treatment targets for plaque psoriasis. Journal of the American Academy of Dermatology, 90(1), 145–158. https://doi.org/10.1016/j.jaad.2023.08.101