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PSORIASIS: A COMPREHENSIVE REVIEW OF CURRENT TREATMENTS AND EMERGING THERAPIES FOR DISEASE MANAGEMENT

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Abstract

Psoriasis is the type of one of the most prevalent forms of chronic inflammatory skin diseases globally with prevalence rates of 0.11 -1.58% and prevalence among the global population of 125 million patients. The review offers an in-depth analysis of the existing knowledge about the pathophysiology of psoriasis, its clinical presentation, and treatment. Psoriasis immunopathogenesis focuses on the interleukin-23/T- helper 17 cell axis, and the recent developments have explained the intricate interrelationship between innate and adaptive immune responses. Therapy modes currently used include topical therapy, phototherapy, traditional systemic therapy and biologic therapy which are aimed at particular cytokine pathways. The biologics landscape has radically changed with the introduction of tumor necrosis factor-alpha, interleukin-12/ 23, interleukin-17, and interleukin-23 biologics, which are showing never-before-seen disease clearance. Newer treatment modalities such as Janus kinase-signal transducer, next-generation biologics, and microbiome-targeted therapies are assured to enhance patient outcome further. This review summarizes the existing evidence on the treatment algorithms, special population issues and the new paradigm of personalized medicine in the management of psoriasis. The combination of biomarkers, genetic profiling, and therapeutic drug monitoring is the future trend towards optimal choice of treatments and the attainment of lasting disease remission. Even though this has been achieved to a greater extent, there are still certain challenges in accessing treatment, long-term safety, and the ultimate cure of the disease instead of managing it.

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1. Introduction

1.1 Definition and Clinical Significance of Psoriasis

Psoriasis is immune-mediated chronic inflammation diseases with excessive growth of keratinocytes and complicated changes in the capacities of the skin barrier. The disorder can be characterized by well-deliminated erythematous plaques with silvery scale, which is, however, not a clear-cut case of how it can be clinically manifested in different individuals with the condition (Boehncke and Schoen, 2015). In addition to the dermatological manifestations, psoriasis is a system inflammatory disorder that has important aspects of overall health and quality of life. The disease is relapsing-remitting and can be characterized with various intervals of aggravation and different intervals of improvement or clearance.

The medical value of psoriasis goes much deeper than aesthetics. The condition provides significant physical burden such as pruritus, pain, and bleeding, and at the same time, psychological wellbeing and social functioning. More recent theoretical frameworks introduce psoriasis as a paradigm immune-mediated disease and studies of the pathogenesis have provided important lessons to be applied in other inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis (Nestle et al., 2009). Social stigma and discrimination are further added to the disease burden since skin lesions can be seen as well as on the skin.

1.2 Global Burden: Epidemiology and Prevalence

Psoriasis is also estimated to impact 2-3 percent of the world population although it is more common in certain geographical areas and ethnicities. Systematic reviews reveal an estimated prevalence of 0.11 to 1.58 in the world, with some 125 million affected globally (Parisi et al., 2013). Greater prevalence rates are seen in populations of northern Europe than African, Asian, and some Indigenous American populations, which indicates that there is a genetic and environmental interaction in disease susceptibility.

Epidemiology of psoriasis provides significant information on the age of onset, gender distribution as well as the severity of the disease. It has a higher incidence in people below the age of 40 years with a minor peak in the age bracket of 50-60 years (Langley et al., 2005). No uniform gender predilection is observed, but studies indicate that it is slightly more prevalent in females, which may have been a consequence of differences in the health-seeking behavior. Psoriasis has a significant economic burden and direct medical expenses, productivity loss, and indirect expenses cost in billions of dollars per year in the developed healthcare systems (Kimball et al., 2015).

1.3 Impact on Quality of Life and Psychosocial Aspects

Psoriasis often has a greater effect on the quality of life than other chronic medical conditions. Medical patients who experience moderate-to-severe psoriasis report equivalent quality of life issues as those found in cancer, diabetes, and heart disease (Rapp et al., 1999). The Dermatology Life Quality Index is always shown to reduce the quality of life significantly in physical, psychological, and social areas. Apparent changes on the exposed skin surfaces cause social anxiety, depression and decreased self esteem and about 20-30 percent of patients develop clinically significant depression (Kurd et al., 2010).

Psychosocial comorbidities are of crucial but often underestimated conditions of psoriasis management. This long-term nature and unpredictability of the flares of the diseases cause a lot of psychological distress. The most common ones are employment discrimination, social isolation, and impaired intimate relationships. A significant percentage of patients have sexual dysfunction whose severity of the disease is associated with reduced sexual quality of life (Gupta & Gupta, 1997). The stigma on visible skin disease remains even with the heightened awareness in the population and requires the integrated provision of psychological assistance as a part of psoriasis care.

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1.4 Associated Comorbidities: Beyond the Skin

Psoriasis is no longer being acknowledged as an isolated inflammatory disease but a multicomorbid systemic disease. The prevalence of psoriatic arthritis associated with the skin disease is 20-30 percent, and most often it starts within 10 years of a skin rash but sometimes before the skin appearance (Gladman et al., 2005). The arthritis has various patterns such as involvement of distal interphalangeal joints, dactylitis, enthesitis, and spondylitis, which can only be managed through rheumatological cooperation.

The most severe comorbidity is cardiovascular disease, psoriasis provides independent risk factors of myocardial infarction, stroke, and cardiovascular mortality (Gelfand et al., 2006). The association of elevated cardiovascular risk also seems to be proportional to the severity of the disease and major adverse events of the cardiovascular outcomes were 58 times higher in severe psoriasis compared to the controls. Components of metabolic syndrome such as obesity, diabetes mellitus and dyslipidemia and hypertension are highly prevalent among psoriatic patients, indicating that there are common inflammatory pathways. There are also increased instances of non-alcoholic fatty liver disease, chronic kidney disease, and some malignancies, which require a detailed screening and prevention methodology (Armstrong et al., 2014).

1.5 Objectives and Scope of This Review

This general review will be used to generalize up-to-date evidence of psoriasis pathophysiology, clinical manifestation and interventions in the treatment of the disorder. The review includes both the well-nullified treatment modalities and the newly developed therapies, and the emerging field of the personalized medicine paradigm in particular. Particular population groups such as pediatric, pregnant women, and aged are given special attention. Biomarkers, treatment algorithms and future research directions can be integrated to give a framework of optimizing clinical decision-making. Through integrating the current knowledge in the realm of basic science, clinical trials, and real-world evidence, the present review aims to enlighten professionals on the evidence-based management strategies and define the gaps in knowledge and the future opportunities of therapeutic strategies.

2. Clinical Manifestations and Classification

2.1 Plaque Psoriasis: The Predominant Presentation

Psoriasis vulgaris/ plaque psoriasis is the most common clinical subtype with 85-90% of all psoriasis cases. Typical lesions appear in the form of well-delineated erythematous plaques that have silvery-white micaceous scale. The scale is an indication of parakeratosis consisting of nuclei that are retained in the stratum corneum indicating the increased epidermal turnover characteristic of psoriatic skin. The sizes of the plaques range between small papules to large confluent plaques greater than 20 centimeters in diameter.

Plaque psoriasis distribution pattern is based on characteristic predilection sites. Extensor areas such as elbows and knees are typical areas of location, but lumbosacral lesion is common as well as scalp and nails. Koebner phenomenon is a process in which new psoriatic lesions form at the areas of cutaneous trauma, which happens in about 25 percent of patients and is a diagnostic finding (Weiss et al., 2002). The thickness of the plaque and the level of erythema and the amount of scales are dependent on the activity of the disease and location. The chronic plaques might acquire central clearance areas or develop hyperkeratotic and cracked one especially on the palm and soles.

2.2 Guttate Psoriasis

Guttate psoriasis is an epidemic form of psoriasis that displays symptoms of a drop-like papules and plaques of 0.5-1.0 centimeters diameter. The name is based on the Latin gutta, which means drop, and it represents the morphology. The subtype is mainly common among children and young adults and often occurs as a sequel of streptococcal pharyngitis by 2-3 weeks. The implication of the connection between Streptococcus pyogenes infection and the mechanisms of molecular mimicry or superantigen-mediated immune activation is that it is a pathogenic process.

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Lesions are spread symmetrically on the trunk and proximal extremities and usually spares the palms, soles and nails. Guttate psoriasis can be the first phase of psoriasis in patients who later acquire chronic plaque disease or a acute exacerbation in patients with the chronic psoriasis. In most cases, the spontaneous resolution happens within 3-4 months, but early antibiotics against underlying streptococcal infection and topical, or phototherapy can hasten the clearance (Wilson et al., 2003).

2.3 Inverse Psoriasis

Inverse or intertriginous psoriasis or flexural psoriasis is a skin condition that affects skin folds such as the axillae, inframammary, groin, and the gluteal cleft. The intertriginous regions are typically warm and moist and the normal morphology of plaque is altered to create smooth, sharply-delimited patches of erythema with no typical scale. Symptoms are worsened by moisture and friction, and common complications are maceration and fissuring.

It is a subtype that occurs in about 3-7 percent of patients with psoriatic and often combines with other subtypes. Lack of scales can slow down the diagnosis, and lesions can be confused with candidal intertrigo, erythrasma or contact dermatitis. The treatment needs altered strategies as it has a higher absorption and the possibility of steroid-induced atrophy in the thin-skinned flexural regions. Topical calcineurin inhibitors can be used as the first-line therapy in a large number of patients with inverse psoriasis (Menter et al., 2009).

2.4 Pustular Psoriasis

Pustular psoriasis is a group of dissimilar clinical entities that have sterile pustules on erythematous bases. Generalized pustular psoriasis (also known as von Zumbusch type), is a rare, yet potentially fatal type of psoriasis, which is featured by pustule activity on a large-scale basis, systemic inflammation, and high hospitalization rates. Acute GPP is characterized by fever, malaise, and sterile pustule sheets converting into pus lakes, and possible effects are electrolyte imbalances, sepsis, and cardiovascular collapse.

Localized disease Localized forms include palmoplantar pustulosis, in which recurrent pustules develop on palms and soles, and acrodermatitis continua of Hallopeau, which occurs on distal digits and nail beds. The IL-36 pathway has a primary role in the pathogenesis of GPP, and mutations in the IL36RN gene encoding the IL-36 receptor antagonist have been found in both familial and sporadic cases (Onoufriadis et al., 2011). More recent therapeutic developments against IL-36 signaling are likely to aid the difficult subtype.

2.5 Erythrodermic Psoriasis

Erythrodermic psoriasis is the most extreme clinical finding, which is characterized by the generalized erythema of over 90% of body surface area. This is a rare manifestation that occurs in less than 2% of psoriatic patients yet a dermatological emergency that needs urgent treatment. Patients present with severe erythema, scaling, and systemic with fever, chills and malaise.

Pathophysiology includes colossal cutaneous vasodilation and disturbed thermoregulation, and all of them have high-output cardiac failure, loss of proteins, and infection risks. Factors that precipitate them are the sudden removal of systemic corticosteroids or immunosuppressants, severe sunburn, infection, and stress. Supportive care, fluid therapy and systemic therapy often require hospitalization. Mortality rates are close to 10 percent, which indicates the level of severity of this manifestation without relevant treatment (Boyd & Menter, 1989).

2.6 Nail Psoriasis and Scalp Involvement

The effects of nail psoriasis include 50-80% of people with plaque psoriasis and is the sole expression 5-10%. The clinical manifestations are pitting, onycholysis, oil-drop discoloration, subungual hyperkeratosis, and splinter hemorrhages. Psoriatic arthritis is closely associated with nail involvement which acts as a clinical indicator of the risk of joint disease. Nail matrix and bed inflammation induce typical changes which could result in severe functional deficiency and cosmetic issues.

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Scalp psoriasis can be experienced by as many as 80% of the patients who end up having the disease. The lesions spread past the hairline on the forehead, neck and postauricular regions and the thick, adherent scale can result in considerable pruritus and loss of hair. Scalp involvement is also very visible and adds to psychological distress. Problems of treatment are the use of medication with hair and the possibility of cosmetic interference with topical treatment (van de Kerkhof et al., 1998).

2.7 Psoriatic Arthritis: Clinical Features and Classification

The development of psoriatic arthritis (PsA) in 20-30 percent of psoriasis patients is a heterogeneous inflammatory arthritis with a wide clinical profile. Classification Criteria of Psoriatic Arthritis (CASPAR) are used to provide the diagnosis, and the inflammatory joint, entheseal, or spinal disease must have three points or more out of a series of established criteria such as current psoriasis, actual or family history of psoriasis, dactylitis, juxta-articular new bone formation, rheumatoid factor negativities, and nail dystrophy (Taylor et al., 2006).

There are five clinical patterns that include asymmetric oligoarthritis, symmetric polyarthritis similar to rheumatoid arthritis, distal interphalangeal joint predominant arthritis, arthritis mutilans with severe bone resorption, and spondyloarthritis with sacroiliitis. Sausage digit or Dactylitis is a hallmark of diffuse inflammation of the joint with synovitis, tenosynovitis, and edema of the soft tissue. Enthesitis, inflammation in the insertions of tendons and ligaments is common in Achilles tendon and plantar fascia. The interval between skin and joint disease has an average of 10 years but in 15 percent, arthritis is the first to occur before skin disease which requires increased clinical attention.

Table 1: Clinical Subtypes of Psoriasis – Characteristics, Distribution, and Prevalence

Subtype	Clinical Features	Typical Distribution	Prevalence	Special Considerations
Plaque psoriasis	Well-defined, raised, red plaques with silvery scales	Extensor surfaces, scalp, lumbosacral	85-90%	Most common form; Koebner phenomenon
Guttate psoriasis	Small, drop-like papules	Trunk, proximal extremities	<10%	Often post-streptococcal; acute onset
Inverse psoriasis	Smooth, erythematous patches	Flexural areas, axillae, groin	3-7%	Moisture and friction aggravate; diagnostic challenges
Pustular psoriasis	Sterile pustules on erythematous base	Generalized or localized	Rare	Life-threatening in generalized form; IL-36 pathway involvement
Erythrodermic	Diffuse erythema involving >90% BSA	Generalized	Rare	Medical emergency; thermoregulatory compromise

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Subtype	Clinical Features	Typical Distribution	Prevalence	Special Considerations
Nail psoriasis	Pitting, onycholysis, oil spots	Fingernails, toenails	50-80%	Associated with PsA; functional impairment

3. Etiology and Risk Factors

3.1 Genetic Predisposition: Polygenic Inheritance Pattern

Psoriasis has great genetic predisposition and twin studies estimate hereditability to be 60-90%. The risk of recurrence among first-degree family members is about 10 percent, and rises to 30 percent when both parents are infected and 50-70 percent when one of the parents has psoriasis and other is psoriatic arthritis (Elder et al., 2010). The complicated inheritance pattern is characterized by numerous locus of susceptibility and small single locus effects, which is in line with the polygenic threshold model.

More than 60 susceptibility loci of psoriasis have been found using genome-wide association studies, involving immune regulatory genes, skin barrier function, and innate immune signaling pathways. The highest genetic risk is carried in the major histocompatibility complex region on chromosome 6p21.3 and the greatest separate risk was carried with HLA-C06:02. There is earlier age of onset, more severe disease, and improved response to some treatment with carriers of HLA-C06:02, which implies some pharmacogenetic uses (Nair et al., 2006).

3.2 Key Susceptibility Loci and Signaling Pathways

In addition to HLA-C, susceptibility loci are contained in the genes that control nuclear factor-kappa B (NF-κB) signaling, phosphoinositide 3-kinase (PI3K)/Akt pathways, and interferon signaling. The IL-12/23 subunits and their receptor are confirmed by IL12B and IL23R genes, which are essential in pathogenesis. NF-kB regulatory protein A20 (TNFAIP3) and IL-17 receptor signaling (TRAF3IP 2), are additional examples that highlight the role of an innate immune dysregulation.

The damage to epidermal pore barrier function due to genetic variation of epidermal differentiation complex genes, such as LCE3B and LCE3C, indicates one of the factors that contribute to the development of the disease. Late cornified envelope gene deletions can damage cutaneous protection against environmental stimuli, allowing the activation of the immune system in genetically susceptible individuals (de Cid et al., 2009). The overlap of immune and barrier functional genetic risk factors contributes to a model of cutaneous injury or infection in susceptible hosts activating an aberrant immune response.

3.3 Environmental Triggers and Modulating Factors

Genetic vulnerability interacts with the environment to cause or increase the severity of disease. Streptococcal infections, especially pharyngitis caused by Streptococcus pyogenes, are well-established guttate psoriasis and plaque exacerbating agents. The temporal relationship indicates that streptococcal antigens and keratinocyte proteins are molecular mimicry or that the activation of T-cells is through superantigen.

In patients, psychological stress is believed to cause psoriasis in 40-80% and stress management interventions have been shown to have a modest level of effectiveness in clinical studies. The stress effects on cutaneous inflammation are mediated

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by the hypothalamic-pituitary-adrenal axis, sympathetic nervous system and local neuroimmune interactions. Koebner phenomenon is triggered by physical trauma and some drugs such as beta-blockers, lithium, antimalarials and interferon can trigger or complicate the disease. Smoking and drinking have been shown to be associated with risk and severity of psoriasis, which may be due to the inflammatory and oxidative stress processes (Armstrong et al., 2014).

3.4 Somatic Mutations and Clonal Expansion

The new developments have found the lesional lesional psoriatic skin to be somatic, thus defying the classical perception of psoriasis being purely autoimmune. Deep sequencing shows that there are clonal expansions of epidermal differentiation, tumor suppressive, and DNA damage response genes in the form of keratinocytes with mutations in NOTCH1, NOTCH2, TP53, FAT1, and PPM1D (Li et al., 2019). These mutations are observed early in the development of the plaques and they persist in the course of treatment indicating that they play a role in the pathogenesis of the disease and as opposed to secondary changes.

The autoimmune/autoinflammatory/ somatic mutation debate demonstrates the changing perception of the heterogeneity of psoriasis. Somatic mutations could cause competitive advantages to clones of mutant keratinocytes, which would allow the persistence and recurrence of the plaque. The paradigm shift implies that there is a potential of clone-directed treatment involving specific genetic changes but clinical application is still in the developmental stage.

3.5 CARD14 Mutations and Familial Psoriasis

CARD14 (caspase recruitment domain family member 14) mutagenesis leads to familial psoriasis, pityriasis rubra pilaris and mutagenic inheritance of these diseases in individual pedigrees. CARD14 is a protein that is expressed in the keratinocyte and regulates the activation of NF-KB. Gain-of-function mutations lead to constitutive NF-c-B signaling, which promotes hyperproliferation and chemokine secretion of the keratinocytes without adaptive immune activation (Jordan et al., 2012).

Psoriasis due to CARD14 mutations in families is associated with early disease, severe disease that is usually unresponsive to standard treatment. The CARD14 association with the disease confirms that NF-kB signaling is a therapeutic target in psoriasis and indicates that some but not all forms of psoriasis are secondary immune activation disorders of keratinocytes. This is a genotypephenotype relationship that shows how genetic stratification can be used to make personalized choices of treatment.

4. Immunopathogenesis of Psoriasis

4.1 Overview of Innate and Adaptive Immune Interactions

Psoriasis pathogenesis is characterized by a complex of crosstalk between the innate and adaptive immune systems, and both of the compartments are necessary in the development and maintenance of the disease. The present paradigm assumes that environmental stimuli activate resident immune cells in hereditary predisposed skin, leading to the cascades of cytokine that recruit and activate adaptive immune cells. The subsequent effect of these cells consists of the production of effector cytokines that lead to hyperproliferation of the keratinocytes and prolonged inflammatory operation.

The psoriasis skin immune system is exceptionally plastic and redundant. T-lymphocytes are dominant in established lesions whereas the others are plasmacytoid dendritic cells, myeloid dendritic cells, macrophages, mast cells, and innate lymphoid cells that play a role in both early and advanced disease stages. These cell type interactions form self-sustaining inflammatory cycles that are not easily interrupted through therapy. These complicated interactions have been understood that has led to the creation of specific biologic therapies that have never been as effective (Nestle et al., 2009).

4.2 The IL-23/Th17 Axis: Central Pathogenic Pathway

The IL-23/T-helper 17 (Th17) axis is the predominant mechanism of immunopathogenesis

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of psoriasis. Dendritic cells and macrophages use intrinsic IL-23, a heterodimeric cytokine consisting of p19 and p40 subunits to produce IL-23 in response to microbial stimuli and endogenous danger signaling. Th17 cells, a subset of CD4+ T-cells, generate IL-17A, IL-17F, IL-22 and other pro-inflammatory cytokines, and differentiate and maintain this phenotype through the action of IL-23.

The cytokine products and T17 cells coordinate the psoriatic phenotype. IL-17A and IL-17F mediate the action on keratinocytes provoking proliferation, neutrophil chemotaxis, and antimicrobial peptides. There is the synergisement between IL-22, which enhances epidermal hyperplasia and prevents terminal differentiation, and IL-17. The effectiveness of IL-23 and IL-17 targeting biologics confirms this as the main treatment option in psoriasis (Langley et al., 2014). There is more evidence, based on genetic observations that the centrality of IL-23 signaling is supported by implicating IL23R and IL12B.

4.3 Role of Dendritic Cells and Keratinocytes in Disease Initiation

Dendritic cells play an important role as coordinators of psoriatic inflammation. Plasmacytoid dendritic cells of early psoriatic lesions secrete type I interferons in response to antimicrobial peptide-DNA complexes through the activation of Toll-like receptor 9. These interferons stimulate myeloid dendritic cells which differentiate and travel to draining lymph nodes to process antigen and ship them to naïve T-cells.

Keratinocytes become active contributors of psoriatic inflammation instead of passive targets. When IL-17, IL-22, and TNF-a are stimulated, keratinocytes secrete chemokines such as CXCL1, CXCL8, and CXCL20 which attract neutrophils, Th17 cells, and dendritic cells. This forms positive feedback loops that trigger and maintain inflammation. Keratinocyte-secreted antimicrobial peptides such as LL-37-complex with self-DNA to stimulate the action of plasmacytoid dendritic cells, the barrier malfunction is connected to the immune activation (Lande et al., 2007).

4.4 Key Cytokines: TNF-α, IL-17, IL-22, and IL-23

Tumor necrosis factor-alpha (TNF- a) is a pleiotropic cytokine that plays various roles in psoriasis. TNF-alpha is produced by macrophages, dendritic cells and T-cells, and it activates endothelial cells, recruits leukocytes, and combines with IL-17 and IL-22 to boost Keratinocyte responses. The extraordinary effectiveness of the TNF class of inhibitors created proof-of-concept that cytokines could be used in treating psoriasis and transformed the mode of therapy.

Th17 cells are the major producers of IL-17A and IL-17F, which also are produced by γδ T-cells, mast cells, and neutrophils, and directly trigger the pro-inflammatory mediators of the keratinocytes. The epidermal hyperplasia and acanthosis are stimulated by the Th22 cells and other lymphocytes as it is stimulated by IL-22. One of its functions is to sustain the presence of Th17 cells and make the cells pathogenic. These cytokines are hierarchically related with IL-23 being upstream of IL-17 and IL-22, which informed the development of specific biologics, and the higher efficacy of IL-23 blockers in head-to-head studies (McGeachy et al., 2019).

4.5 The IL-36 Pathway in Generalized Pustular Psoriasis

The IL-36 cytokine family is stored in the pustular variants of psoriasis. The IL-36 family members that are produced by keratinocytes and immune cells are IL-36α, IL-36, and IL-36 γ, and stimulate pro-inflammatory activity via the IL-36 receptor. IL-36 receptor antagonist (IL-36Ra) is a regulator of IL-36 signaling, and IL36RN loss-of-function mutations lead to unmitigated IL-36 stimulation and GPP.

The IL-36 signaling increases neutrophil recruitment and activation, which explains the high pustule in the patients affected. The IL-36 also stimulates the IL-23 production by the dendritic cells, connecting the IL-36 and IL-23/Th17 pathways. Spesolimab is an anti-IL-36 receptor antibody that was recently approved as GPP and confirms that genetic findings can be

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translated into clinical therapeutics (Bachelez et al., 2019).

4.6 Amplification Loops and Chronic Inflammation

The persistence of psoriasis is due to the formation of vicious circles of inflammation, which cannot be interrupted by a simple therapeutic procedure. Cytokines released by keratinocytes attract and stimulate immune cells, which release more cytokines which in turn stimulate further release of cytokines by keratinocytes. This forms a vicious circle of inflammation, which is perpetuated without permanent therapeutic assistance.

The role of epigenetic changes in psoriatic keratinocytes and immune cells could be responsible in the chronicity of the disease. Phenotypic alterations that are produced by DNA methylation modifications, histone modifications, and altered patterns of microRNA expression become stable even after the prompting event. The resident memory T-cells developed in healed lesions might cause the recurrence to be rapid when discontinuing treatment or when exposed to the trigger. Such processes define the relapsing-remitting characteristic of psoriasis and the necessity of maintenance therapy used by most of the patients (Cheuk et al., 2014).

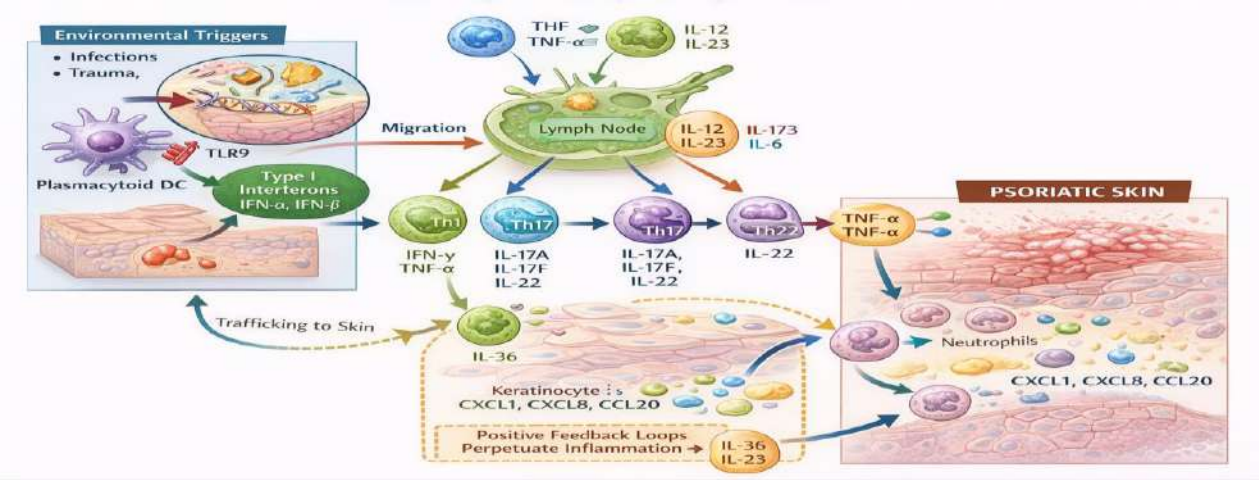

Figure 1: Schematic Representation of Psoriasis Immunopathogenesis

Environmental triggers (infection, trauma) activate plasmacytoid dendritic cells (pDCs) via TLR9 recognition of LL37-DNA complexes. pDCs produce type I interferons (IFN-α/β), activating myeloid dendritic cells (mDCs) that migrate to lymph nodes. Naïve CD4+ T-cells differentiate into Th1, Th17, and Th22 subsets under the influence of IL-12, IL-23, and IL-6. Effector T-cells traffic to skin, producing TNF-α, IL-17, IL-22, and IFN-γ. These cytokines stimulate keratinocyte hyperproliferation and chemokine production (CXCL1, CXCL8, CCL20), recruiting neutrophils and additional T-cells. Positive feedback loops involving keratinocyte-derived IL-36 and IL-23 perpetuate inflammation.

5. Diagnosis and Assessment

5.1 Clinical Diagnosis: History and Physical Examination

Psoriasis is a disease whose diagnosis is mainly based on clinical evaluation, morphology and distribution of the disease are normally characteristic and therefore allow diagnosis to be made without further investigations. A detailed history must capture age of onset, duration of the disease, family history, precipitating factors, prior treatments and response as well as effects on quality of life. The patient has signs of joint pain, such as morning stiffness, dactylitis, or enthesitis, which is enough to consider psoriatic arthritis.

Physical examination involves a thorough systematic method of examination of each part of the body such as the scalp, nails, intertriginous

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areas and genitals usually ignored by the common examination. Lesion morphology, distribution and extent should be documented. Linear lesions with a history of previous trauma may be used to provoke the Koebner phenomenon. Psoriatic arthritis is assessed by examining peripheral joints, assessment of dactylitis in digits, examination of entheseal sites and the motion of the axial skeleton.

5.2 Dermoscopic Features

Dermoscopy improves the diagnostic accuracy and helps to differentiate between psoriasis and eczematous dermatitis, lichen planus and other papulosquamous diseases. Typical appearances are dotted vessels that are uniformly distributed on a red background, which are the depiction of the dermal papillary vessels that are enlarged and long. White scales can be found, but the thickness of scales is dependent on the chronicity of the lesions and the location of anatomical sites.

Other dermoscopy observations are the red dot appearance of the glomerular vessels, the white shiny streaks that symbolize confluent parakeratosis, and the existence of blood spots which symbolize pinpoint bleeding following removal of scale (Auspitz sign). Nail psoriasis dermoscopy shows splinter hemorrhages, distal onycholysis (oil drop) and irregular pitting. The characteristics help in the diagnosis in cases of an atypical clinical presentation and allow tracking the response of the treatment process on the microscopic level (Lallas et al., 2013).

5.3 Histopathology When Indicated

Histopathological examination of the skin biopsy proves diagnosis in case of the ambiguous clinical presentation. Histological characteristics are typical epidermal acanthosis and rete ridge elongation, parakeratosis with neutrophil collections (Munro microabscesses), spongiform pustules of Kogoj, and long and thickened dermal papillae. The granular covering is usually reduced or lacking.

T-lymphocytes comprise the dermal infiltrate, whereby CD4+ cells are predominant in the initial lesion and CD8+ cells in the established plaque. Neutrophils are deposited at the epidermis and stratum corneum. Histopathology differentiates psoriasis with lichen planus, spongiotic dermatitis and secondary syphilis. In erythrodermic psoriasis, the typical appearance can be suppressed, and clinical-pathological correspondence is necessary.

5.4 Disease Severity Assessment Tools

Assessment of objective severity helps determine what treatment to use, and it allows the monitoring of the response to therapy. Psoriasis Area and Severity Index (PASI) is the gold standard of clinical trials with a scoring system of erythema, induration, and scale (0-4 scale) on four body parts (head, trunk, upper limbs, lower limbs) with surface area involvement. Efficacy endpoints that are commonly used include PASI 75 (75% improvement compared to baseline) and PASI 90 (90% improvement).

The Physician Global Assessment (PGA) gives the severity of the global clinical impression as clear to severe. The palm-as-1% rule is a quantitative measure of extent which is easy to estimate using Body Surface Area (BSA). Dermatology Life Quality Index (DLQI) measures patient outcomes, including the symptoms, functioning, and emotional impact, which is patient-reported. Treat-to-target strategies become more guided by composite measures with both objective and patient-reported outcomes (Pariser et al., 2007).

5.5 Screening for Psoriatic Arthritis

Due to its prevalence and with the possibility of joint destruction, psoriatic arthritis needs to be screened systematically in all psoriasis patients. PEST (Psoriasis Epidemiology Screening Tool) and Psoriatic Arthritis Screening and Evaluation (PASE) are questionnaires that are used to screen patients who need rheumatological assessment. The most important screening questions refer to joint pain, morning stiffness, dactylitis, enthesitis, and changes of nails.

Psoriatic arthritis diagnosis should be timely, since there exists a window of opportunity, based on which the joints can be treated before permanent damage occurs. Dermatologists are advised to have low rheumatology referral thresholds especially on patients with nail psoriasis, obese patients, and those with widespread skin involvement.

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Multidisciplinary dermatology-rheumatology care is the best way to treat patients with skin and joint disease.

5.6 Comorbidity Assessment and Monitoring

The overall treatment of psoriasis involves consideration of related comorbidities. It must be assessed on baseline by taking body mass index, waist circumference, cardiovascular risk factors, and blood pressure. Examples of laboratory screening include fasting glucose or hemoglobin A1c, lipid profile, and liver function tests. Patients who have the risk factors or symptoms need further analysis of psoriatic arthritis, non-alcoholic fatty liver disease, and depression.

Consistent checkups would help to identify comorbidities early enough and treat. Biannual cardiovascular risk assessment, regular screening of diabetes and continuous monitoring of psoriatic arthritis symptoms is routine care. Comorbidity management can be integrated into the psoriasis management algorithms to enhance patient outcomes in general and potentially alter the severity of psoriasis by implementing weight loss and quitting smoking among other interventions.

Table 2: Disease Severity Classification and Treatment Implications

Severity	PASI Score	BSA Involvement	DLQI Score	PGA	Recommended Treatment Level
Mild	<10	<10%	<10	Clear/Minimal	Topical therapy as first-line; phototherapy if inadequate
Moderate	10-20	10-20%	10-18	Mild-Moderate	Phototherapy, conventional systemic agents, or biologics based on patient factors
Severe	>20	>20%	>18	Severe	Biologics or combination therapy; consider hospitalization for erythrodermic variants

6. Treatment Overview and Therapeutic Goals

6.1 Goals of Treatment: Clearance, Quality of Life, and Long-term Control

Modern psoriasis therapy targets complete or near-complete clearance of the skin, as it has been acknowledged that ongoing disease activity is associated with impaired quality of life and risk of comorbidity. The treat-to-target paradigm, which is based on the management of rheumatoid arthritis, employs certain objectives such as PASI 3 or BSA 1% are achieved in the 3-6 months after the commencement of the treatment. The accomplishment of these targets predicts improved future results and lessened comorbidity weight.

Improvement of the quality of life is an equally significant therapy outcome, since objective clearance but the absence of functional and emotional recovery is an unsuccessful outcome of treatment. Patient-reported outcomes such as DLQI, work productivity, and sexual health ought to be measured on a regular basis. Avoiding disease flares allows patients to be able to work, have relationships and social lives since long-term disease management with acceptable safety profiles and minimum treatment burden can be used (Strober et al., 2020).

6.2 Step-care Approach Versus Treat-to-Target

Conventional step-care methods only become more intense when the less aggressive treatments have failed. Nevertheless, this plan can expose patients to long-term disease under control and the resulting quality of life defect and

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development of comorbidities. The paradigm of treat-to-target therapy focuses on the prompt attainment of the pre-established therapeutic outcomes by selecting the initial therapy correctly and ensuring it is timely to change the treatment of non-responders.

Implementation of treat-to-target necessitates periodic disease activity measurement, precise targets of treatment, and arbitrary algorithms of poor response. It might be more resource-intensive in the short term, but this method can prove to be cost-effective due to a decrease in hospitalization rates, work productivity, and comorbidities. Step-care and treat-to-target should be based on the disease severity, patient preferences, comorbid conditions, and resources available in the healthcare system (Armstrong and Read, 2020).

6.3 Shared Decision-Making and Patient Preferences

The best treatment of psoriasis involves the active involvement of patients in the decision-making process. Shared decision-making combines the clinical evidence on efficacy and safety with patient values and preferences with life situations. The burden on treatment such as the frequency of dosing, the route of administration, monitoring needs, and cost ought to be discussed openly.

There are significant differences in patient preferences when it comes to acceptable trade-offs between efficacy and safety, convenience and cost. Other patients can be fast clearance oriented and can accept injection administration and monitoring necessities and others prefer oral or topical therapy even though they are less effective. Knowing the goals of each patient allows an individual to select treatment that maximizes compliance and satisfaction. Educational resources and decision aids are useful in assisting patients to take informed therapeutic decisions (Léaute-Labreze et al., 2014).

6.4 Treatment Algorithm Based on Severity and Comorbidities

The use of treatments is a combination of the severity of the disease and comorbidity profile of the patient together with patient specificities and access to medications. Topical therapy is a first-line treatment of mild disease, and phototherapy should be used when the response is insufficient or when there is deep involvement. Systemic therapy in moderate-severe disease, biologics are first-line therapy in a large percentage of patients because they are more effective and have more desirable safety profiles than conventional systemic therapy.

The comorbidities have a great impact on the choice of treatment. Psoriatic arthritis patients need combinations of skin and joint disease therapies with preference given to TNF inhibitors, IL-17 inhibitors or IL-23 inhibitors rather than apremilast or phototherapy therapies. Cardiovascular disease is a disease that should pay close attention to NSAID use and could play a role in biologic selection. Obesity decreases the effects of some biologics, which favors weight management programs. Listed Inflammatory bowel disease is a contraindication of IL-17 inhibitors due to possible increased disease. These comorbidity considerations are incorporated as personalized treatment algorithms (Menter et al., 2019).

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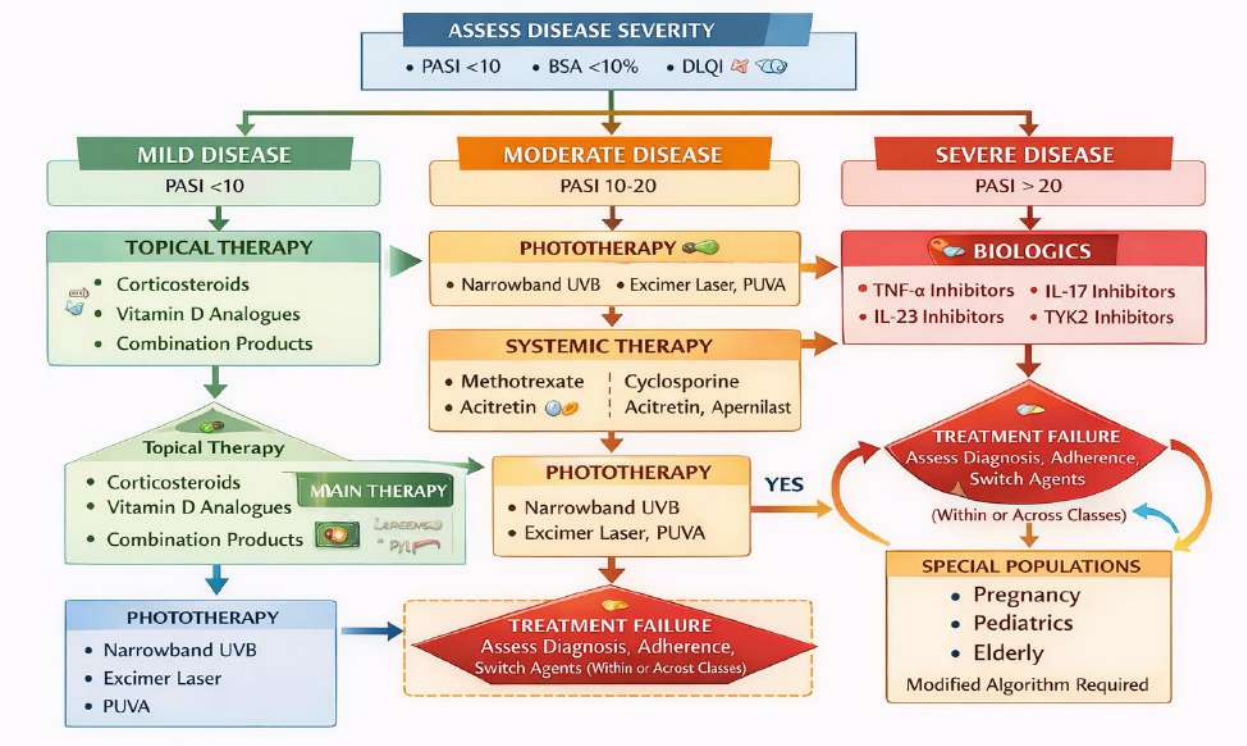

Figure 2: Psoriasis Treatment Algorithm Based on Disease Severity

Assessment of disease severity using PASI, BSA, and DLQI guides initial therapy selection. Mild disease (PASI <10, BSA <10%) begins with topical therapy including corticosteroids, vitamin D analogues, and combination products. Inadequate response after 8-12 weeks or patient preference triggers transition to phototherapy or systemic therapy. Moderate disease (PASI 10-20) may initiate with phototherapy or conventional systemic agents (methotrexate, cyclosporine, acitretin, apremilast), with biologics considered for inadequate response or significant quality of life impairment. Severe disease (PASI >20) warrants biologic therapy as first-line, with selection based on comorbidities, patient preference, and access. Treatment failure at any level triggers reassessment of diagnosis, adherence, and switching to alternative agents within or across classes. Special populations including pregnancy, pediatrics, and elderly patients require modified algorithms.

7. Topical Therapies

7.1 General Measures: Emollients, Soap Substitutes, and Scale Removal

Basic skin care practices are the basis of psoriasis management in all grades of the disease. Topical application of emollients on a regular basis decreases scaling, increases the barrier activity and the penetration of active topical agents. Emollients in the form of ointments are better at providing better occlusion and hydration than creams or lotions, especially when it comes to chronic plaques. Patients are to be advised about generous and regular application, and some may be suggested to use plastic wrap overnight so as to increase their efficiency.

The effects of alkaline cleansers on impaired skin barriers are avoided by soap substitutes. Bath oils and emollient washes can be washed without depriving the natural lipids. Scale loss will help to ease medication absorption and decrease pruritus. Keratolytic agents, such as salicylic acid (2-10) and urea preparation soften and exfoliate scale but caution must be taken to prevent excessive irritation or systemic salicylates absorption. Topical therapy is most effectively achieved by

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gentle mechanical scale removal on the skin during bathing and then applied with emollients immediately (Menter & Griffiths, 2007).

7.2 Corticosteroids: Potency Classes, Applications, and Limitations

Topical corticosteroids are still the most commonly prescribed in treating psoriasis and its effect is dependent on the potency and formulation as well as duration of use. It is classified into seven potency classes (I-VII, where I is superpotent) to be selected properly depending on the anatomical location and the disease severity. The use of superpotent steroids (clobetasol propionate, betamethasone dipropionate) has proven to be efficient in thickness of plaques on trunk and extremity, with lower strength agents being used on face, flexures and maintenance therapy.

Anti-inflammatory action of corticosteroids is caused by the inhibition of the production of cytokines, T-cell activation, and vasoconstriction. Nevertheless, there are restrictions such as the tachyphylaxis, skin atrophy, the formation of the striae, and the rebound flare during the discontinuation, which limit long-term use. The weekend therapy or pulse dosing plans are the remaining ways of ensuring remission without causing significant side effects. Non-pharmacological combination with vitamin D analogues allows a reduction in steroid dose and better long-term results. Patients need to be taught about the right applied quantity (fingertip unit) and time to achieve the best effects with the least adverse effects (local and systemic) (Lebwohl, 2003).

7.3 Vitamin D Analogues: Calcipotriol, Calcitriol, and Tacalcitol

Vitamin D analogues are the use of vitamin D analogue as first-line treatment of mild to moderate psoriasis and also as maintenance therapy. These agents attach to vitamin D receptors on keratinocytes and immune cells, differentiating, proliferating, and producing cytokines. The most comprehensively investigated analogue, calcipotriol (calcipotriene), has a similar efficacy to mid-potency corticosteroids and has a good safety profile with a long-term usage.

Calcipotriol is used in two applications on the body, one in ointment, cream, or scalp solution formulations at 0.005%. The highest dose per week (100g) has been shown to prevent hypercalcemia, but is uncommon to limit clinical practice. The first adverse effect is local irritation, especially of facial and intertriginous skin. Co-formulation with betamethasone dipropionate in single-product formulations increase their efficacy, minimize irritability, and ease regimens. Alternatives are available that have potentially fewer irritation effects, such as calcitriol and tacalcitol which should be used in sensitive regions (Mason et al., 2013).

7.4 Combination Products: Calcipotriol/Betamethasone Dipropionate

Combined products of calcipotriol and betamethasone dipropionate show better effect than either of the two agents used alone, and their effects are fast acting and benefit-sustaining. The combination uses hyperproliferative and inflammatory aspects of psoriasis and reduces the number of corticosteroids-related adverse effects by dosage reduction. The daily application is found to be better than the twice daily monotherapy regimen when it comes to adherence.

Clinical trials show PASI75 response rate of about 60 percent with 4 weeks of combination therapy and marked improvement of quality of life measures. The scalp psoriasis suspension formulation concerns the problem of topical agent delivery through hair. The long-term studies confirm 52 weeks of the continuity of use with proper monitoring. This association is one of the foundations of topical therapy of trunk and limb psoriasis and the generic formulations enhance access (Kragballe et al., 2009).

7.5 Topical Calcineurin Inhibitors for Sensitive Areas

As steroid-sparing agents, tacrolimus ointment (0.03 per cent, 0.1 per cent) and pimecrolimus cream (1 per cent) may be used in facial, intertriginous, and genital psoriasis cases when

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atrophy of the skin and other body regions due to corticosteroids is of great concern. These agents block T-cell activation through calcineurin which lowers inflammation but does not cause skin thinning. Although not powerful enough to treat plaque psoriasis than corticosteroids, they are especially useful in treating inverse psoriasis and facial cases.

Twice-daily use yields benefits in 60-80% of patients using it in facially and intertriginously located psoriasis after 8 weeks. Transient burning and pruritus are some of the common adverse effects which usually subside with continued usage. The black box warning about the possible risk of malignancy, which was caused by the studies on animals and theoretical concerns, has not been proved by the wide scope of post-marketing surveillance or epidemiological researches. However, regulatory issues can be resolved by providing proper patient guidance and restricting its application to the specified locations (Gribetz et al., 2004).

7.6 Coal Tar and Dithranol Preparations

Conventional antipsoriatic agents, such as coal tar and dithranol (anthralin) are not obsolete in modern practice, especially in resource constrained environments. Coal tar preparations decrease the inflammation and the scale by the effects on the DNA synthesis inhibition and antimicrobial effects. Several different formulations of crude coal tar (1-5%), refined tar extracts (liquor carbonis detergens) exist, but cosmetic acceptability constrains compliance.

Dithranol (0.1-3%) suppresses mitochondrial activity and causes free radicals, which suppress the growth of keratinocytes. Ingram regimen is a combination of dithranol using UVB phototherapy. Contemporary therapy involves short-contact therapy (30 minutes to 2 hours) that minimizes irritation but does not impair therapeutic effect. The staining of the skin, clothing and the fixtures in the bathroom is a major drawback. These classical therapies are an effective alternative therapeutic means in the absence of newer ones, which are contraindicated (Thami and Sarkar, 2002).

7.7 Site-Specific Management Strategies

Best topical therapy involves accommodation to characteristics of anatomical sites. Plaques on the trunk and limbs respond to high doses of corticosteroids and vitamin D analogues but using ointment vehicles is preferred with chronic lesions. The head is a special problem due to hair impediment; solutions, foams, and sprays enhance the penetration, and overnight occlusions will increase the penetration. Salicylic acid shampoos help to remove the scale before active therapy.

Facial, flexural and genital skin demand low intensity or non-steroidal agents with higher absorption, and future atrophy. Calcineurin inhibitors are the first-line agent of most patients with low-potency short-term steroids during exacerbations. Multi-site combination methods are better than a single site approach because they enhance the results. The level of adherence and satisfaction is improved through patient education on site-specific regimens and expectations.

7.8 Novel Topical Formulations: Sprays, Foams, and Gels

The development of formulation technology has enhanced cosmeticability and convenience of topical therapy application. Aerosol foams and sprays allow to apply them evenly on vast surfaces and hairy areas without the greasy effect of the old-fashioned ointments. Fixed-combination calcipotriol/betamethasone aerosol foam proves to be more effective and more preferred by patients than the conventional ointments and is also fast-drying and leaves no residue.

Corticosteroids and vitamin D analogues can be administered in gel formulations to provide an option to patients who want the products that are not greasy. The technology of nanoemulsion and microemulsions improves drug absorption and steers off irritation. These advances in formulations are dealing with the issue of adherence that is associated with cosmetic acceptability, which might enhance real-world effectiveness more than it is shown in clinical trials involving conventional vehicles (Lebwohl et al., 2015).

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Table 3: Topical Therapies for Psoriasis – Formulations, Potency, and Application Guidance

Drug Class	Examples	Formulations	Potency/Strength	Application Frequency	Common Side Effects
Corticosteroids	Hydrocortisone	Ointment, cream	Mild (Class VII)	1-2x daily	Skin atrophy, telangiectasia, striae
	Betamethasone valerate	Ointment, cream, scalp application	Potent (Class III)	1x daily	As above, hypothalamic-pituitary-adrenal axis suppression
	Clobetasol propionate	Ointment, cream, shampoo, foam	Very potent (Class I)	1-2x daily (short course)	As above, rebound flares, folliculitis
Vitamin D analogues	Calcipotriol	Ointment, cream, scalp solution	0.005%	1-2x daily	Local irritation, hypercalcemia (rare, dose-dependent)
Combination	Calcipotriol/betamethasone dipropionate	Ointment, gel, suspension, foam	0.005%/0.064%	1x daily	Irritation, steroid-related effects, pruritus
Calcineurin inhibitors	Tacrolimus	Ointment	0.03%, 0.1%	2x daily	Burning, pruritus, erythema (transient)
	Pimecrolimus	Cream	1%	2x daily	As above, headache (rare)

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Drug Class	Examples	Formulations	Potency/Strength	Application Frequency	Common Side Effects
Keratolytics	Salicylic acid	Ointment, shampoo, gel	2-10%	As needed	Irritation, systemic toxicity with extensive use
	Urea	Cream, ointment	10-40%	1-2x daily	Stinging, irritation

8. Phototherapy

8.1 Historical Perspective and Mechanisms of Action

Phototherapy treatment of psoriasis dates back almost a hundred years, and it was observed that the sun exposure of the lesions enhanced the situation, which resulted in systematic use of the artificial light sources. Phototherapeutic benefit mechanisms include immunosuppression, apoptotic pathogenic T-cells induction, and inhibitory effects on keratinocyte proliferation. The ultraviolet (UV) radiation adjusts the cutaneous cytokine profiles to eliminate pro-inflammatory mediators and increase the anti-inflammatory signals.

The therapeutic window of psoriasis capitalizes on the dissimilarity of action of UV radiation on the pathological and normal skin cells. UVB waves (290-320 nm) are absorbed by the epidermis, which directly influences Keratinocytes and Langerhans cells. UVA has a deeper penetration (320-400 nm) and thus it needs photosensitizers (psoralens) in order to be therapeutic. Non-ionizing phototherapy today is customized to maximize the efficacy and minimize the carcinogenesis risks by optimization of wavelength use, dosing schedules and optimal cancer safety (Kurd and Gelfand, 2009).

8.2 Types of Phototherapy: Modalities and Mechanisms

Broadband UVB (BB-UVB, 290-320 nm) was the original modality of phototherapy, although this has been mostly replaced by more targeted methods. Narrowband UVB (NB-UVB, 311-313 nm) is a less erythemogenic and carcinogenic therapy compared to BB-UVB because of the therapeutic wavelengths it emits. The NB-UVB is the new first-line phototherapy in psoriasis in moderate-to-severe cases as it has a good efficacy and safety profile.

Psoralen plus UVA (PUVA) is a combination of oral or topical 8-methoxypsoralen and UVA therapy that results in photosensitization which increases treatment efficacy. PUVA has very high clearance as compared to UVB but has more risks such as nausea, phototoxicity, and risk of skin cancer. The excimer laser (308 nm) is applied directly to each individual plaque without treating the immediate adjacent healthy skin and allows higher dosage. This method is applicable to those patients with limited disease or recalcitrant plaques (Ibbotson et al., 2010).

8.3 Clinical Efficacy: Response Rates and Outcomes

NB-UVB elicits 60-80% of responses with PASI75 in 20-30 sessions and clearance is usually attained in 2-3 months. Response rates are associated with cumulative dose and frequency of treatment with

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thrice-weekly giving the best results. PUVA is also more effective with PASI75 scores of 80-85, but the inconvenience and safety limitations restrict its modern-day effectiveness. The NB-UVB home units can obtain similar outcomes to the office-based treatment in the right patients.

The excimer laser generates rapid resolution of the plaque, 70-80 percent of the plaques treated with excimer laser can be cleared in 10-12 sessions. Its use is however restricted to those patients who have comparatively few plaques due to the time these patients take to treat the lesions individually. The combination methods such as phototherapy with topical agents or systemic therapy improve response rates and could decrease cumulative UV dose needed to achieve clearance (Almutawa et al., 2013).

8.4 Treatment Protocols and Dosing

Phototherapy therapy is administered in a standardised regimen to achieve the best effect and the fewest number of burns. The initiation of NB-UVB is usually set at 70-80% of minimal erythema dose (MED) or set suberythemogenic doses, varied by 10-20 percent in regard to response to treatment and erythema. Three times per week is a good compromise frequency of treatment, but more visits can be considered more effective in clearing the patient.

PUVA must be taken in the form of oral 8-methoxypsoralen which is taken 1.5-2 hours prior to exposure to UVA, dosage varying according to weight and skin type. The doses of UVA used in the beginning are 0.5-2.0 J/cm 2, spaced at 0.5-1.0 J/ cm2. Sun avoidance 24-hours of treatment and use of protective eyewear are required. The treatment is continued until clearance or maximum response, and then it is followed by maintenance therapy or switching to other treatment methods to manage the disease long-term.

8.5 Home Phototherapy Versus Office-Based Treatment

Home NB-UVB units offer a substitute to an office-based therapy and enhance the accessibility of patients who have a low mobility, living in an isolated area, or strict time schedule. Safety measures in modern home units have been made such as keyed operation, dose programming, and treatment timers. The results of studies show similar effectiveness of home phototherapy and office phototherapy, high patient satisfaction, and long-term cost-efficiency.

Selection criteria to use to choose patients under home phototherapy are reliability, self-administerability of treatment, and access to the follow-up care. Education about the correct technique, the side effects and the time to visit providers is necessary. Home phototherapy is safely implemented with the help of remote monitoring of teledermatology. Although the initial cost of equipment is high, the long-term benefit of saving travel time and other healthcare consumption is in favor of home therapy among the right patient choices (Koek et al., 2009).

8.6 Combination with Topical or Systemic Agents

The use of phototherapy with topical agents or systemic agents may increase efficacy and minimise cumulative UV exposure. Pre-UVB topical calcipotriol enhances response rates and speeds up clearance. Combination of systemic retinoids (acitretin) and phototherapy (Re-PUVA) have the benefit of decreasing the required dose of psoralen and potentially decreasing risk of skin cancer. The use of Methotrexate and UVB is helpful in patients who needed prompt clearance.

Biologics used in combination with phototherapy is still under investigation and there is a subject of concern regarding the possible photocarcinogenicity. Nevertheless, there are data which indicate that biologics will allow reduced doses of phototherapy to keep clearance. The combination approaches must strike a balance between improvement in efficacy and complexity, cost and possible adverse effects. A standard approach is sequential therapy comprising of phototherapy during induction and maintenance with topical or systemic agents (Menter et al., 2010).

8.7 Safety Considerations and Long-term Risks

Phototherapy has the disadvantages of acute adverse effects such as erythema, blistering and

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phototoxic reactions. The chronic effects are photoaging, pigmentary alterations, and cancer. NB-UVB has a good safety profile and low probability of skin cancer in majority of the studies, but long term and high dosage exposure can lead to higher risk of squamous cell carcinoma. PUVA has dose-related risks of squamous cell carcinoma, basal cell carcinoma and melanoma that are well-documented and restrict its use as first-line treatment.

During any type of phototherapy, ocular protection is required to avoid the formation of cataracts. The use of male genital protection at PUVA decreases the risk of squamous cell carcinoma at this location. Frequent screening of the skin cancer among patients who have experienced much exposure to phototherapy is required. The advantages of phototherapy in managing severe psoriasis should be measured using these risks and informed consent should capture the long-term effects (Archier et al., 2012).

8.8 Contraindications and Patient Selection

Photosensitizing disorders (xeroderma pigmentosum, lupus erythematosus) or the presence of melanoma or widespread non-melanoma skin cancer and the use of photosensitizing drugs are considered absolute contraindications of phototherapy. Relative contraindications are fair skin types put at high risk of burns, incapability of standing or adhering to positioning needs, and pregnancy (in PUVA). Phototherapy is associated with the risk of skin cancer among patients who have been treated with arsenic or been exposed to ionizing radiation.

The criterion used in the selection of the patient is disease severity, distribution, past treatment responses, and lifestyle. Phototherapy is appropriate when the disease is widespread and the patient can tolerate UV, when he/she does not want systemic or topical therapy and is undergoing adjunctive therapy using topical agents or systemic agents. Patient availability and motivation are needed because of the time commitment (2-3 sessions per week during 2-3 months). In the event that phototherapy is not possible or feasible, alternative or adjunctive treatments should be considered

Table 4: Comparison of Phototherapy Modalities

Modality	Wavelength	Efficacy (PASI75)	Advantages	Disadvantages	Safety Concerns
BB-UVB	290-320 nm	~50-60%	Widely available, inexpensive	Lower efficacy, frequent visits, longer courses	Photoaging, minimal skin cancer risk
NB-UVB	311-313 nm	60-80%	Superior to BB-UVB, well-tolerated, no photosensitizer required	Requires frequent office visits, time-intensive	Photoaging, minimal cancer risk with standard protocols
PUVA (oral)	320-400 nm	80-85%	High efficacy, durable remissions	Nausea, ocular protection requirements, photosensitivity, time-consuming	Increased NMSC and melanoma risk, photoaging, pigmentation

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Modality	Wavelength	Efficacy (PASI75)	Advantages	Disadvantages	Safety Concerns
Excimer laser	308 nm	70-80% (localized)	Targeted treatment, fewer sessions, spares unaffected skin	Limited to localized disease, time per lesion, higher cost	Local burning, blistering, pigmentary changes

9. Conventional Systemic Agents

9.1 Methotrexate: Mechanism, Dosing, Monitoring, and Safety

Methotrexate has a long history of clinical use and is proven to be effective and safe in the treatment of systemic psoriasis with more than 50 years of clinical experience. The medication prevents the dihydrofolate reductase, disrupting cell renewal and duplication of DNA. This is caused by immunosuppressive effects caused by inhibition of aminoimidazole carboxamide ribonucleotide transformylase resulting in the buildup of adenosine that has anti-inflammatory effects. Moderate-severe psoriasis can be successfully treated with low dose-based weekly methotrexate (7.5-25mg).

Once-week oral or subcutaneous injections result in PASI75 responses in about 40 per cent of patients in 12-16 weeks. Folic acid supplementation (1-5 mg daily, with exception of methotrexate dosage on the day of intake) lowers GIT toxicity and hepatic enzyme increases and does not diminish its efficacy. The monitoring should include baseline and regular complete blood count, liver tests, and kidney tests. The main long-term issue is hepatotoxicity, and liver biopsy is traditionally advised with cumulative doses of 1.5-3.5 grams of the drug, however, non-invasive methods such as FibroScan are also gaining popularity (Warren et al., 2009).

The contraindications are pregnancy, breastfeeding, severe hepatic or renal insufficiency, and acute infections. Certain NSAIDs and probenecid should be closely reviewed when interacting with the medication, as well as trimethoprim-sulfamethoxazole. Nevertheless, methotrexate continues to play a significant role in the management of psoriasis, especially in patients with psoriatic arthritis where it offers them the benefits of joint protection not available using all biologics.

9.2 Cyclosporine: Rapid Onset, Short-term Use, and Renal Monitoring

Cycophosphamide is a calcineurin inhibitor that gives fast control of the disease by suppressing T-cells and cytokine secretion. This drug interacts with cyclophilin preventing the process of dephosphorylation of nuclear factor of activated T-cells (NFAT) through the calcium second messenger, calcineurin, preventing the transcription of IL-2 and the proliferation of T-cells. This effect yields dramatic efficacy in 2-4 weeks and therefore cyclosporine is useful in severe flares, erythrodermic psoriasis, and pustular psoriasis.

Starting dose is 2.5-5 mg/kg/day in two doses and titration should be based on the response and tolerability. PASI75 rates approach 70-80% at 12-16 weeks. Limitations to long-term use, however, include nephrotoxicity and hypertension; sustained treatment is typically used in 12-24 months. Safe administration is guided by blood pressure checks, serum creatinine test, and trough level test. A 30 per cent rise in serum creatinine compared to baseline or onset of hypertension requires a reduction or termination of the dose (Mrowietz et al., 2011).

Cyclosporine is mainly used as induction or rescue therapy in the severe disease, followed by the switch to maintenance agents after the control is

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obtained. Many drug interactions such as contraindication with statins metabolized by CYP3A4 should be thoroughly examined as a result of medication. Its acute exacerbation prevents cyclosporine, especially in severely-ill or fluctuating patients without any prior hospitalization, but its usage in chronic treatment has been overshadowed by biologic alternatives.

9.3 Acitretin: Oral Retinoid, Teratogenicity, and Mucocutaneous Effects

Second-generation oral retinoid acitretin is used to regulate epidermal differentiation and immune activity via nuclear retinoic acid receptor. Normalization of keratinocyte proliferation, neutrophil migration, and Th17 cell differentiation are prevented by the drug. Acitretin has a small PASI response (30-50%), which is combined with phototherapy (Re-PUVA) or other drugs, thereby improving efficacy.

The worst adverse effect of acitretin is its teratogenic properties and pregnancy prevention measures are obligatory in female patients with a childbearing potential. The half life of its elimination is long meaning that it needs 3 years of contraception after discontinuation. The mucocutaneous effects such as cheilitis, xerosis and alopecia are typical and may be controlled with emollients and dose modification. Hepatotoxicity and hyperlipidemia should be monitored, and acitretin should not be prescribed with notable hepatic dysfunction or hyperlipidemia that is not controlled (Saurat et al., 2015).

Acitretin has specific application in pustular psoriasis, palmolar psoriasis and as a steroid-sparing agent in erythrodermic disease. Immunosuppression is absent, thus can be used in patients with malignancy history or chronic infection. Phototherapy uses can reduce the retinoid doses and UV exposure with combination and maximize the risk-benefit profile of suitable candidates.

9.4 Apremilast: Phosphodiesterase 4 Inhibitor and Safety Profile

Apremilast is a phosphodiesterase 4 (PDE4) inhibitor that is the first oral small-molecule drug approved to treat psoriasis and psoriatic arthritis, and it raises intracellular levels of cyclic AMP. This leads to a reduction of pro-inflammatory (TNF- 0, IL-17, IL-23) and anti-inflammatory (IL-10) mediators. Apremilast is a good alternative to injectable therapy when patients are having the contraindications to biologics or prefer an oral route of administration.

The ESTEEM trials showed that the PASI75 rates were 33% at the end of week 16, and both nail psoriasis and psoriatic arthritis symptoms were improved. Although its efficacy is lower than that of biologics, apremilast has the following benefits: there is no need to monitor the laboratory status, there is no immunosuppression, and it is safe enough in patients with a history of malignancy. Side effects are diarrhea, nausea, headache and depression which are mostly mild and self-limiting. A reduction in weight by 5-10% is seen in certain patients and they may have some benefits to patients with metabolic comorbidities (Papp et al., 2015).

Apremilast is more appropriate in patients with moderate disease who have not succeeded with topical therapy, patients with contraindications to biologic or conventional systemic treatment and in combination with topical or phototherapy. Its ease of administration that does not need injections or intravenous fluids is attractive to a significant number of patients, but affordability and the lack of significant efficacy discourages first-line use in severe disease.

9.5 Fumaric Acid Esters

The Fumaric acid esters (FAEs), which have been in use in Europe over decades, are also approved by regulatory authorities in a number of countries, including the United States. Dimethyl fumarate and analogues are immunomodulators, which affect immune responses in several ways such as prevention of nuclear factor-kappa B, induction of T-cell apoptosis and stimulation of Th2-type responses. Delayed-release formulation is better than older compounds in gastrointestinal tolerability.

Clinical trials show that 35-40 percent of patients respond to PASI75 after 16 weeks, and the responses are sustained after 24 weeks.

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Lymphopenia especially on CD4+ and CD8+ T-cells need monitoring but does not usually need discontinuation. The adverse effects include gastrointestinal (diarrhea, abdominal pain, nausea) and flushing which usually subside with continuous use or dose adjustment. With related compounds, progressive multifocal leukoencephalopathy has also been reported in multiple sclerosis but has not been observed in patients with psoriasis although the condition should be monitored (Reich et al., 2017).

FAEs provide patients with oral option to non-biologic systemic therapy and have different safety profile as compared to immunosuppressive agents. The access in certain areas gives more choice of therapy, although there is still access problems in some markets.

9.6 Comparative Efficacy and Safety of Conventional Systemic Agents

There is little information comparing head-to-head among traditional systemic agents, most of the information is obtained through placebo-controlled trials and network meta-analysis. Cyclosporine is the fastest-acting with the highest toxicity in the long run. Methotrexate provides a better balance of effectiveness, safety and affordability to most patients and specifically in psoriatic arthritis it is more beneficial. Acitretin does not show potent effects in monotherapy of psoriasis of the plaque form, but offers special value in palmoplantar psoriasis.

The safety profiles of Apremilast and FAEs have been found to be better than those of methotrexate and cyclosporine but the efficacies are lower. The option between the traditional agents is based on the disease nature, presence of comorbidities, patient preference, and regulatory availability. In modern practice, these agents may frequently act as bridges to biologic therapy, combination partners or biologic contraindicated patients.

9.7 Indications for Systemic Therapy

Moderate-to-severe psoriasis (PASI >10, BSA >10 per cent or major impact on quality of life) not responding to topical therapy is an indication of systemic therapy, and all patients with severe disease irrespective of the past treatments. Other clues are psoriatic arthritis, which needs systemic treatment, which is erythrodermic or generalized pustular psoriasis, or notable nail or palmoplantar, which affects functionality.

The patient-related factors affecting the choice of systemic therapy include comorbidities (hepatic, renal, cardiovascular disease), pregnancy intentions, history of malignancies, risk of infections, and polypharmacy. Biologics are now extremely effective and have decreased the number of barriers to initiating systemic therapy, with treat-to-target programs indicating a preference for early vigorous treatment to avoid the development of comorbidities and progression of the disease.

9.8 Combination Strategies and Rotational Therapy

Combination therapy will increase efficacy and may decrease individual agent doses and toxicities. Methotrexate can be used together with biologics (especially TNF inhibitors), acitretin in combination with phototherapy and apremilast in combination with topical agents. Combination of methotrexate and biologics can aid in lowering immunogenicity and improving response to partial responders.

Rotational therapy switches agents in order to reduce cumulative toxicity, especially in the case of cyclosporine and phototherapy. Nevertheless, the efficacy and safety of biologics are superior and have diminished the need to adhere to complicated rotation protocols in most patients. There should be close attention to drug interactions and cumulative adverse effects when using combination and rotation strategies, and individual approaches need to be applied depending on the treatment history and the response patterns.

10. Biologic Therapies

10.1 Introduction to Biologic Therapy in Psoriasis

Biologic therapies have revolutionized the management of psoriasis with unprecedented effectiveness in the control of the disease and improvement of quality of life. Biologics are a type of protein-based therapeutic that is generated

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using the recombinant DNA technology and is used to address particular molecular mediators of psoriatic inflammation. Biologic agents have limited off-target toxicity with specific action in the pathogenic pathways in contrast to the conventional systemic agents, which have broad immunosuppressive effects.

Biologics evolution came after understanding of the psoriasis immunopathogenesis, and every successive target confirmed the basic research mechanistic hypotheses. TNF-alpha inhibitors provided evidence of concept in cytokine targeting, and later IL-12/23, IL-17 and IL-23 agents have increasingly enhanced the treatment of the disease. The biologic era implies the shift of the paradigm of symptomatic treatment to disease modification that, according to some evidence, could prevent the development of comorbidity (Griffiths et al., 2015).

10.2 TNF-α Inhibitors: Pioneers of Targeted Therapy

The earliest biologic to be used to treat psoriasis is tumor necrosis factor-alpha inhibitors, which include adalimumab, etanercept, infliximab, and certolizumab pegol. These agents complex with soluble and /or membrane-bound TNF-alpha and block their receptors and downstream inflammatory responses. The suppression of TNF-Alpha decreases the activation of the keratinocytes, expression of the endothelial adhesion molecules, and the actions of Th1/Th17 cells.

The fully human anti-TNF monoclonal antibody adalimumab subcutaneously every other week reports PASI75 in about 70-80% of patients by week 16. Etanercept is a TNF receptor fusion protein (two doses a week) that yields PASI75 in 45-50 percent of the patients, and weekly dosing is also offered as a maintenance therapy. Infliximab, a monoclonal intravenous chimeric antibody, has the quickest onset that reaches PASI75 levels over 80 percent after week 10, but, with immunogenicity, the results are not long lasting. A PEGylated Fab fragment called certolizumab pegol provides an option of monthly maintenance therapy with similar efficacy as adalimumab (Menter et al., 2011).

Safety concerns are the risk of more infections, especially tuberculosis and severe bacterial infections, which are to be screened and monitored. Lymphoma, exacerbation of heart failure, and demyelinating disease are rather uncommon risks that require a careful choice of the patients. The formation of antidrug antibodies and immunogenicity diminishes the efficacy in some patients, which proves benefits in combination with methotrexate or replacing other agents. Irrespective of these factors, TNF inhibitors have continued to play an essential role especially in psoriatic arthritis where they are demonstrated to have benefits of established joint protection.

10.3 IL-12/23 Inhibitors: Ustekinumab

Ustekinumab is a human monoclonal antibody that binds to the p40 subunit of IL-12 and IL-23 which is an important development in the treatment of psoriasis. Ustekinumab interferes with various pathogenic processes simultaneously by preventing the differentiation of Th1 and the maintenance of Th17 in the presence of IL-12 and IL-23, respectively. It is conveniently dosed subcutaneously during week 0, 4, and subsequently with intervals of 12 weeks.

Phase 3 trials showed a PASI75 of 66-76 per cent at week 12, and a response rate persists 5 years after the trials. Ustekinumab demonstrates a specific efficacy in patients who have had an unsatisfactory response to TNF inhibitors, with PASI75 in about half of TNF-experienced patients. This is due to the positive safety profile with low infection rates compared to TNF inhibitors as well as the absence of any reported high risk of malignancy (Long-term maintenance therapy, 2013).

The mechanism of action or action places ustekinumab between general immunosuppression and more specific IL-23-specific immunosuppression. Although extremely successful, the later invention of p19-specific IL-23 blockers have shown better activity and ustekinumab is today being used as an alternative in case these more modern inhibitors are not available or contraindicated.

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10.4 IL-23 Inhibitors (p19 Subunit): Superior Efficacy and Convenience

The p19 subunit-specific IL-23 inhibitors—guselkumab, risankizumab, and tildrakizumab—represent the current standard for psoriasis efficacy. By selectively targeting IL-23 without affecting IL-12, these agents potently suppress Th17-mediated inflammation while preserving IL-12-dependent antimicrobial defenses. This selectivity may contribute to the favorable infection profiles observed with this class.

Guselkumab, administered subcutaneously at weeks 0, 4, and then every 8 weeks, achieved PASI90 in approximately 70% and PASI100 in 35-40% of patients at week 16 in the VOYAGE trials. Risankizumab, dosed at weeks 0, 4, and every 12 weeks thereafter, demonstrated PASI90 in 75% and PASI100 in 40-50% of patients in the ULTIMMA and SUSTAIN studies, with sustained responses over 2 years. Tildrakizumab, administered every 12 weeks after initial dosing, produces PASI75 in approximately 65-70% of patients (Reich et al., 2017; Gordon et al., 2018).

Head-to-head trials demonstrate superiority of IL-23 inhibitors over TNF inhibitors and ustekinumab. Risankizumab achieved higher rates of complete clearance than adalimumab and ustekinumab in direct comparisons. The convenience of quarterly maintenance dosing, high rates of complete or near-complete clearance, and favorable safety profiles position IL-23 inhibitors as first-line biologic options for many patients with moderate-to-severe psoriasis.

10.5 IL-17 Inhibitors: Rapid Onset and High Efficacy

IL-17 inhibitors—secukinumab, ixekizumab, and brodalumab—target the key effector cytokine of the Th17 pathway, producing rapid and dramatic disease improvement. These agents demonstrate the fastest onset of any biologic class, with significant improvement observed within 1-2 weeks and PASI75 rates approaching 80-90% at week 12.

Secukinumab, a fully human anti-IL-17A monoclonal antibody administered weekly for 4 weeks then monthly, achieved PASI90 in 59% and PASI100 in 24% of patients at week 12 in the ERASURE and FIXTURE trials, with continued improvement to week 52. Ixekizumab, targeting IL-17A with subcutaneous dosing every 2 weeks initially then monthly, produced PASI90 in 71% and PASI100 in 41% of patients at week 12 in the UNCOVER trials. Brodalumab, an anti-IL-17 receptor A antibody blocking signaling from IL-17A, IL-17F, and IL-17E, achieved PASI100 in 37% of patients at week 12 (Langley et al., 2014; Papp et al., 2016).

The rapid onset makes IL-17 inhibitors particularly suitable for patients requiring urgent improvement or those with severe, debilitating disease. However, IL-17 inhibition carries specific risks including mucocutaneous candidiasis (2-4% of patients) and potential exacerbation of inflammatory bowel disease. Screening for IBD history is essential, with caution or avoidance in patients with Crohn's disease or ulcerative colitis.

10.6 Comparative Efficacy: Network Meta-Analyses

Multiple randomized trials provide data that can be used to conduct an indirect comparison between biologic classes through network meta-analyses. These studies have been continually topping the IL-23 and IL-17 inhibitors by efficacy outcome measures such as PASI90 and PASI100 response rates. The highest probabilities of complete clearance are normally observed with risankizumab, guselkumab and ixekizumab, followed by secukinumab and brodalumab.

TNF inhibitors and ustekinumab are less effective than IL-23 and IL-17 inhibitors in network meta-analyses although they still have benefits in certain clinical conditions, such as the management of psoriatic arthritis, and a long-term safety track record. The selection between high-efficacy agents is based on the speed of onset (preferring IL-17 inhibitors), the frequency of administration (preferring IL-23 inhibitors), safety, and patient comorbidities. There is no overall better agent, and it should be selected individually depending on the patient traits and preferences (Armstrong et al., 2020).

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10.7 Safety Profiles and Black Box Warnings

Mechanisms and agents of biologic safety differ. TNF inhibitors have black box warnings of severe infections and malignancies, and the reactivation of the tuberculosis is one of the specific issues that necessitate screening and prophylaxis. There are IL-17 inhibitors, which caution against suicidal ideation and suicide (brodalumab) and infection. Any biologic must be assessed with regard to active infection before starting and during treatment.

The most frequent side effects are the injection site reactions, upper respiratory infections, and headache. Infection rates are 1-3% in classes, with the lowest rates being found with IL-23 inhibitors. The malignancy signals have not been regularly recorded, although long-term follow-ups are going on. TNF inhibitors are rarely associated with cardiovascular events and demyelinating disease as well as lupus-like reactions. Newer agents are generally safer, but in most studies, IL-23 inhibitors have the best risk-benefit ratio (Sbidian et al., 2017).

10.8 Tuberculosis and Hepatitis Screening Before Initiation

All biologic therapy requires screening for latent tuberculosis infection using tuberculin skin testing or interferon-gamma release assays, with chest radiography for positive screens. Latent TB treatment is mandatory prior to biologic initiation. Hepatitis B screening (HBsAg, anti-HBc, anti-HBs) identifies patients requiring antiviral prophylaxis or avoiding certain agents. Hepatitis C screening is recommended given increased prevalence in psoriasis patients and potential treatment interactions.

Live vaccines are contraindicated during biologic therapy, necessitating completion of indicated immunizations prior to initiation. Annual influenza vaccination and appropriate pneumococcal vaccination are recommended. The risk of serious infections requires patient education regarding prompt evaluation of febrile illnesses or infection symptoms. Prophylactic antibiotics are not routinely recommended, though they may be considered for patients with recurrent infections.

10.9 Biologic Switching Strategies: Intraclass Versus Interclass Switching

Failure to respond to initial biologic therapy should be systematically assessed with regards to adherence, antidrug antibody development, and mechanism of failure. The primary non-response (inappropriate improvement at 12-16 weeks) indicates mechanistic insufficiency with a preference to switch interclass to an agent of another target. Follow-up loss of response following initial response might suggest immunogenicity, an idea in favor of intraclass switching or incorporation of methotrexate.

Replacement of the TNF inhibitors with the IL-17 or IL-23 inhibitors has resulted in high response rates, even in those who have not responded to several previous TNF agents. The effectiveness of IL-23 inhibitors in patients who have experienced TNF history justifies the use as second-line therapy. The use of IL-17 and IL-23 inhibitors interchange is not well-supported by data but seems to work in cases of safety or insufficient response. Having multiple agents in each class allows optimization of each patient response (Warren et al., 2020).

10.10 Special Populations: Pregnancy, Pediatrics, and Elderly

Pregnancy planning affects biologic selection, and little information exists regarding the relative safety of TNF inhibitors (especially certolizumab pegol with limited placental transfer) and ustekinumab. Discontinuation of IL-17 and IL-23 inhibitors should be done before conception due to little pregnancy data. The considerations of breastfeeding give preference to low oral bioavailability agents with high molecular size that limits their transfer into milk.

Etanercept, adaliumab and ustekinumab are approved in children in most jurisdictions and are used to treat psoriasis in children. IL-23 inhibitors show a high level of efficacy in trials conducted in adolescents, and their regulatory approvals are expected. The elderly patients have to be carefully evaluated in terms of their comorbidities, and IL-23 inhibitors should be preferred due to a low risk of infections and low drug interactions. Renal or hepatic impairment does not typically require dose

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changes, but specific agent pharmacokinetics are to be examined.

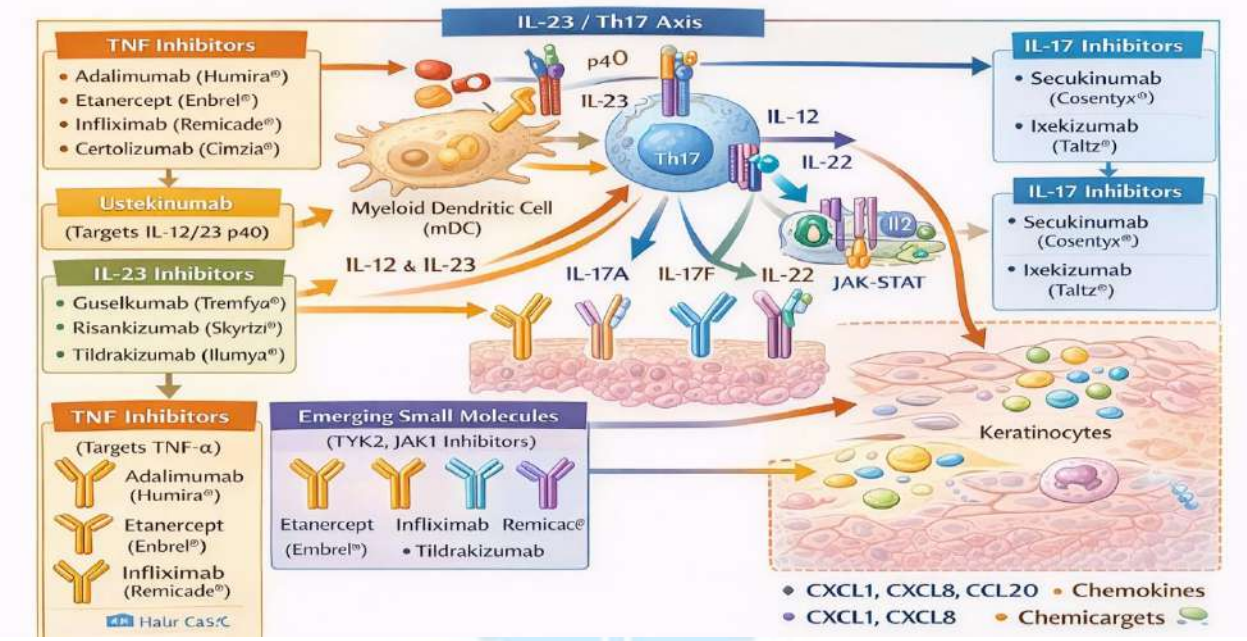

Figure 3: Molecular Targets of Biologic Therapies in Psoriasis

The central IL-23/Th17 axis shows myeloid dendritic cell production of IL-23 driving Th17 cell differentiation. Th17 cells produce IL-17A, IL-17F, and IL-22, acting on keratinocytes to induce proliferation and chemokine production. TNF-α amplifies inflammation through effects on multiple cell types. Therapeutic antibodies are positioned at their molecular targets: TNF inhibitors (adalimumab, etanercept, infliximab, certolizumab) bind soluble and transmembrane TNF-α; ustekinumab binds the p40 subunit of IL-12 and IL-23; guselkumab, risankizumab, and tildrakizumab bind the p19 subunit of IL-23; secukinumab and ixekizumab bind IL-17A; brodalumab binds the IL-17 receptor A. Intracellular signaling cascades including JAK-STAT pathways represent targets for emerging small molecule therapies.

11. Emerging and Pipeline Therapies

11.1 JAK-STAT Pathway Inhibitors

Janus Signaling transducer and activator of transcription (JAK-STAT) is the pathway that conveys the signals of a receptor of various cytokines which play a role in the pathogenesis of psoriasis, such as IL-23, IL-12, and interferons. Oral JAK inhibitors have a benefit of convenience over injectable biologics and also focus on intracellular signaling nodes that are common to several pathogenic cytokines.

The most advanced agent in this group is called deucravacitinib, a selective inhibitor of tyrosine kinase 2 or TYK2. In contrast to non-selective JAK inhibitors, deucravacitinib selectively inhibits TYK2 and shows little JAK1, JAK2, or JAK3 inhibition, which may enhance the safety profile without compromising efficacy due to blocking of IL-23, IL-12, and interferon signaling. Phase 3 trials (POETYK PSO-1 and PSO-2) found that PASI75 was observed in 58 and 36 percent of subjects in week 16, and PASI90 was observed in 36 and 36 percent of subjects in week 16, respectively, and was superior to apremilast and not inferior to secukinumab. Non-selective JAK inhibitors did not exhibit any more occurrences of serious infection, thrombosis, or laboratory abnormalities (Armstrong et al., 2023).

Other TYK2 inhibitors, such as zasocitinib, are in earlier stages of development, and JAK1-inhibitors such as upadacitinib are shown to be effective in psoriasis with the added benefit of being taken by mouth. The JAK inhibitors will be placed based on

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the long-term safety information, and TYK2 selectivity has a potential to provide better risk-benefit profiles than the wider JAK inhibition.

11.2 Next-Generation IL-17 Inhibitors

In head-to-head trials, bimekizumab, which is a monoclonal antibody blocking IL-17A and IL-17F, has been shown to be more effective than secukinumab. PASI90 rates of 85-91% and PASI100 rates of 50-60, respectively, in the BE SURE and BE RADIANT studies were the highest efficacy rates reported in phase 3 psoriasis studies. The IL-17A and IL-17F dual inhibitory effect could be more effective in inhibiting the IL-17-mediated inflammation in totality, but candidiasis rates remain higher compared with the IL-17A-selective agents.

There are other biosimilar or bio-better IL-17 inhibitors under development like Netakimab and this may provide more access and cost reductions. Optimization of IL-17 targeting is ongoing, and studies of other treatment schedules, combination methods and biomarkers to select patients with maximum therapeutic response remain in progress.

11.3 Novel IL-23 Inhibitors

Mirikizumab is a humanized anti-IL-23 p19 antibody that has been shown to have similar levels of efficacy in phase 3 studies to the current IL-23 inhibitors, with PASI90 rates of 60-65% at week 16. The OASIS trials indicate quarterly maintenance with dosing like any other IL 23 inhibitor. Agents within this category of highly effective agents could be distinguished by differences in the antibody engineering or formulation or immunogenicity profiles.

The IL-23 inhibitor category is still growing, with research into ultra-long acting formulations, subcutaneous auto-injectors to enhance patient friendliness and in children. IL-23 inhibition efficacy and safety are high, which makes this mechanism central in the management of psoriasis, and the way it can be delivered and accessed is being optimized.

11.4 Dual and Combination Therapies

The AFFINITY study investigated combination therapy with guselkumab (IL-23 inhibitor) and golimumab (TNF inhibitor) for psoriatic arthritis, demonstrating enhanced skin and joint outcomes compared to monotherapy. While not yet approved, such combinations may address patients with severe, refractory disease or rapid control requirements. The safety of biologic combinations requires careful evaluation given theoretical concerns about additive immunosuppression.

Other combination approaches under investigation include biologics with small molecules, such as IL-17 or IL-23 inhibitors combined with apremilast or deucravacitinib. These strategies aim to enhance efficacy through complementary mechanisms while potentially reducing individual agent doses. The optimal combinations, dosing schedules, and patient selection criteria remain to be defined through clinical trials.

11.5 Microbiome-Targeted Therapies

The cutaneous and gut microbiome alterations observed in psoriasis have prompted investigations into microbiome-modulating therapies. Probiotic supplementation, particularly with *Lactobacillus* and *Bifidobacterium* species, has demonstrated modest improvements in psoriasis severity in small trials, potentially through modulation of systemic inflammation and immune responses. Prebiotic interventions aimed at promoting beneficial bacterial growth are similarly being explored.

Fecal microbiota transplantation (FMT) represents a more aggressive approach to gut microbiome modification. Case reports and small series suggest benefit in severe, refractory psoriasis, though controlled trials are lacking. The mechanisms likely involve restoration of microbial diversity, reduction of pro-inflammatory bacterial species, and enhancement of short-chain fatty acid production with immunomodulatory effects. Safety concerns regarding infection transmission and long-term consequences limit current FMT application to research settings (Navarro-López et al., 2019).

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Topical microbiome modulation through bacterial transplantation or targeted antimicrobial peptides is in early development. The complex interplay between skin microbiota, barrier function, and immune activation suggests that microbiome-targeted approaches may serve as adjunctive rather than standalone therapies, potentially enhancing responses to conventional treatments.

11.6 Metabolic Interventions: GLP-1 Receptor Agonists

The metabolic comorbidities of psoriasis and shared inflammatory pathways linking obesity, insulin resistance, and cutaneous inflammation have prompted investigation of metabolic interventions. Glucagon-like peptide-1 (GLP-1) receptor agonists, widely used for type 2 diabetes and obesity, demonstrate anti-inflammatory effects beyond glycemic control and weight reduction.

Retrospective studies and small trials suggest that GLP-1 agonists may improve psoriasis severity in patients with concurrent diabetes or obesity, potentially through reduction of adipose tissue inflammation, improved insulin sensitivity, and direct effects on immune cells. The LEADER and SUSTAIN cardiovascular outcome trials with liraglutide and semaglutide showed reduced psoriasis exacerbations in diabetic patients, supporting a disease-modifying effect. Dedicated psoriasis trials with GLP-1 agonists are warranted to define their role in metabolic comorbidity management and potential direct effects on skin disease (Egeberg et al., 2018).

11.7 Itolizumab: Anti-CD6 for Plaque Psoriasis

Itolizumab, a humanized monoclonal antibody targeting CD6, has been approved for moderate-to-severe plaque psoriasis in several countries. CD6 is a co-stimulatory molecule expressed on T-cells and natural killer cells, involved in T-cell activation, adhesion, and trafficking. By modulating CD6 signaling, itolizumab reduces T-cell proliferation and pro-inflammatory cytokine production without complete depletion.

Clinical trials demonstrate PASI75 rates of 40-50% at week 12, with a favorable safety profile characterized by low infection rates and no increased malignancy risk. The mechanism differs from cytokine-targeting biologics, offering a potential option for patients with contraindications to other agents or as combination therapy. The availability of itolizumab expands therapeutic options, particularly in regions where other biologics have limited access (Kaur et al., 2019).

11.8 IL-36 Receptor Antagonists for Generalized Pustular Psoriasis

Spesolimab, an anti-IL-36 receptor monoclonal antibody, represents the first targeted therapy approved specifically for generalized pustular psoriasis (GPP). The Effisayil trials demonstrated rapid and dramatic resolution of pustules and systemic inflammation in GPP flares, with significant improvement within one week of single-dose administration. This efficacy validates the IL-36 pathway as the primary driver of GPP pathogenesis and demonstrates the power of mechanism-based therapeutic development.

Imsidolimab, another IL-36 receptor antagonist, has shown similar efficacy in early trials. The availability of targeted therapy transforms GPP management, reducing reliance on high-dose corticosteroids and cyclosporine with their attendant toxicities. Long-term data regarding prevention of flares and safety of repeated dosing will inform the optimal integration of IL-36 inhibitors into GPP treatment algorithms (Bachelez et al., 2021).

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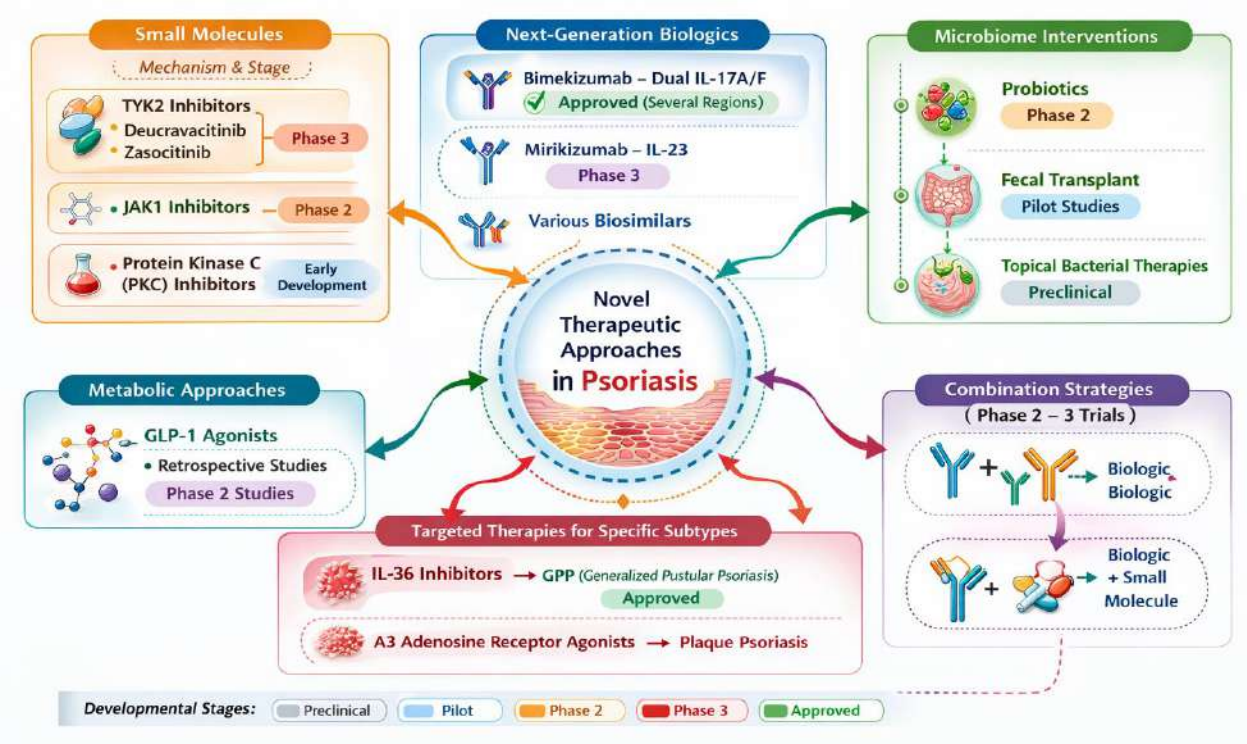

Figure 4: Emerging Therapeutic Targets in Psoriasis

The diagram depicts current developmental therapeutics categorized by mechanism and stage. Small molecules include TYK2 inhibitors (deucravacitinib, zasocitinib) in phase 3, JAK1 inhibitors in phase 2, and protein kinase C inhibitors in early development. Next-generation biologics show bimekizumab (dual IL-17A/F) approved in several regions, mirikizumab (IL-23) in phase 3, and various biosimilars. Microbiome interventions display probiotics in phase 2, fecal transplant in pilot studies, and topical bacterial therapies in preclinical stages. Metabolic approaches highlight GLP-1 agonists in retrospective and phase 2 studies. Targeted therapies for specific subtypes include IL-36 inhibitors for GPP (approved) and A3 adenosine receptor agonists for plaque psoriasis. Combination strategies are represented by biologic-biologic and biologic-small molecule pairings in phase 2-3 trials.

12. Special Populations and Comorbidities

12.1 Pediatric Psoriasis: Treatment Considerations

Pediatric psoriasis affects approximately 1% of children, with significant impact on physical and psychological development. Plaque psoriasis predominates, though guttate and pustular presentations are more common than in adults. Treatment selection must balance efficacy against safety concerns in growing children, with particular attention to effects on growth, bone development, and long-term immune function.

Topical therapies remain first-line for mild disease, with low-to-mid potency corticosteroids and calcineurin inhibitors preferred for sensitive areas. Phototherapy is effective and generally well-tolerated, though compliance with multiple weekly visits challenges school-age children. Systemic therapy is indicated for moderate-to-severe disease, with methotrexate representing the conventional systemic agent with the most pediatric experience. Etanercept is approved for children aged 4 years and older, with adalimumab and ustekinumab approved for adolescents. IL-23

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inhibitors demonstrate excellent efficacy in pediatric trials, with regulatory submissions pending (Paller et al., 2020).

The psychosocial impact of visible skin disease during formative years necessitates integrated psychological support. Family dynamics, school bullying, and adherence challenges require specialized pediatric dermatology expertise. Transition to adult care should be planned to ensure continuity of effective therapy during adolescence.

12.2 Pregnancy and Lactation: Safe Treatment Options

Psoriasis management during pregnancy requires balancing maternal disease control against fetal safety. Disease often improves during pregnancy, particularly in the second and third trimesters, though postpartum flares are common. Topical therapies including low-potency corticosteroids and calcineurin inhibitors are generally safe, though vitamin D analogues should be used cautiously given limited data.

Conventional systemic agents present varying risks: cyclosporine may be used when necessary with blood pressure and renal monitoring; methotrexate and acitretin are absolutely contraindicated due to teratogenicity. Among biologics, certolizumab pegol has minimal placental transfer due to lack of Fc region, making it preferred when biologic therapy is essential. Other TNF inhibitors cross the placenta increasingly in the second and third trimesters, with live vaccine avoidance for exposed infants recommended. IL-17 and IL-23 inhibitors should be discontinued prior to conception given limited data (Yiu et al., 2022).

Breastfeeding considerations favor topical therapies, cyclosporine, and certolizumab pegol. Other biologics have limited transfer into breast milk due to large molecular size, though infant exposure should be minimized by timing dosing away from nursing. The postpartum period requires proactive management given high flare rates and the challenges of caring for a newborn while managing chronic disease.

12.3 Elderly Patients: Comorbidities and Polypharmacy

The prevalence of psoriasis increases with age, and the elderly population represents a growing proportion of patients requiring systemic therapy. Age-related physiological changes alter drug metabolism and increase infection risk, necessitating modified treatment approaches. Comorbidities including cardiovascular disease, renal impairment, and malignancy are more prevalent, influencing therapeutic selection.

IL-23 inhibitors are particularly well-suited for elderly patients given their favorable safety profile and low infection risk. TNF inhibitors require careful screening for heart failure, demyelinating disease, and malignancy. Methotrexate dosing should be reduced for renal impairment, with vigilant monitoring of hematologic and hepatic parameters. Drug interactions with polypharmacy for comorbid conditions require systematic review, particularly with agents metabolized by cytochrome P450 enzymes. The risk of falls and cognitive impairment may affect self-injection capability, supporting caregiver involvement or transition to office-administered therapies (Tang et al., 2020).

12.4 Psoriatic Arthritis: Integrated Management

The presence of psoriatic arthritis fundamentally alters treatment selection, favoring agents with demonstrated joint efficacy. TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors all provide benefit for peripheral arthritis, enthesitis, and dactylitis, with ustekinumab and apremilast showing more modest joint responses. The American College of Rheumatology and National Psoriasis Foundation guidelines recommend treat-to-target approaches for joint disease, aiming for minimal disease activity in both domains.

Coordinated dermatology-rheumatology care optimizes outcomes, with shared decision-making regarding therapeutic priorities when skin and joint responses diverge. Imaging including ultrasound and MRI detects subclinical joint inflammation, informing treatment escalation before irreversible damage occurs. Conventional disease-modifying antirheumatic drugs (DMARDs) including methotrexate and

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sulfasalazine provide limited skin benefit but may be combined with biologics for joint protection or immunogenicity reduction (Coates et al., 2020).

12.5 Cardiovascular Disease and Metabolic Syndrome

Cardiovascular disease represents the leading cause of excess mortality in psoriasis, with systemic inflammation contributing to accelerated atherosclerosis. Treatment selection should consider cardiovascular risk reduction, with TNF inhibitors demonstrating potential cardioprotective effects in some studies. IL-17 and IL-23 inhibitors show neutral cardiovascular profiles, with ongoing trials evaluating specific cardiovascular outcomes.

Metabolic syndrome components require active management, with weight reduction improving both psoriasis severity and treatment response. Bariatric surgery produces dramatic psoriasis improvement in morbidly obese patients. The choice of biologic should consider effects on metabolic parameters, with IL-17 and IL-23 inhibitors showing neutral or beneficial effects on lipids and glucose metabolism. Blood pressure monitoring is essential, particularly with cyclosporine and TNF inhibitors (Gelfand et al., 2018).

12.6 Inflammatory Bowel Disease: Therapeutic Considerations

The epidemiological association between psoriasis and inflammatory bowel disease (IBD) influences treatment selection. IL-17 inhibitors are contraindicated in patients with active or history of Crohn's disease or ulcerative colitis, as IL-17A plays a protective role in intestinal mucosal defense. Cases of new-onset or exacerbated IBD have been reported with IL-17 inhibition.

For patients with concurrent psoriasis and IBD, TNF inhibitors (particularly infliximab and adalimumab) offer benefit for both conditions. Ustekinumab is approved for both psoriasis and Crohn's disease, providing a convenient single agent for patients with both conditions. IL-23 inhibitors demonstrate preliminary efficacy in IBD trials, with potential future positioning for this comorbidity combination. Careful screening for IBD symptoms including unexplained weight loss, abdominal pain, and altered bowel habits should precede IL-17 inhibitor initiation (Habashi et al., 2019).

12.7 Obesity: Impact on Treatment Response

Obesity affects 30-40% of psoriasis patients and reduces treatment response across multiple agents. The mechanisms include increased inflammation from adipose tissue, altered drug pharmacokinetics with increased volume of distribution, and potential neutralizing antibodies with subtherapeutic drug levels. Weight-based dosing of some biologics addresses pharmacokinetic factors, though fixed dosing remains standard for most agents.

Weight loss of 5-10% significantly improves psoriasis severity and enhances biologic response. Dietary modification and exercise programs should be integrated into comprehensive care. For patients with severe obesity and inadequate response to weight-based dosed biologics, bariatric surgery evaluation may be appropriate. The IL-23 inhibitors appear less affected by obesity than other classes, potentially offering advantages for overweight patients (Jensen et al., 2020).

12.8 Malignancy and Infection Risk

The theoretical concern regarding biologic therapy and malignancy risk has not been substantiated by long-term registry data, with no consistent signal for increased solid tumors or lymphoma beyond the baseline psoriasis risk. However, patients with active malignancy or recent treatment were excluded from clinical trials, necessitating individualized risk assessment. For patients with cured malignancy, the interval before biologic initiation depends on cancer type and stage, with dermatologic and oncologic collaboration informing decisions.

Infection risk varies by agent, with IL-23 inhibitors demonstrating the lowest rates of serious infections. TNF inhibitors carry the highest infection risk, particularly in elderly patients and those with chronic lung disease. Screening for hepatitis B and C, HIV, and tuberculosis is mandatory. Herpes zoster vaccination is recommended prior to biologic initiation in

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eligible patients. The COVID-19 pandemic highlighted infection considerations, with most biologics safe to continue during the pandemic though live vaccine avoidance complicates vaccination strategies (Michaels et al., 2021).

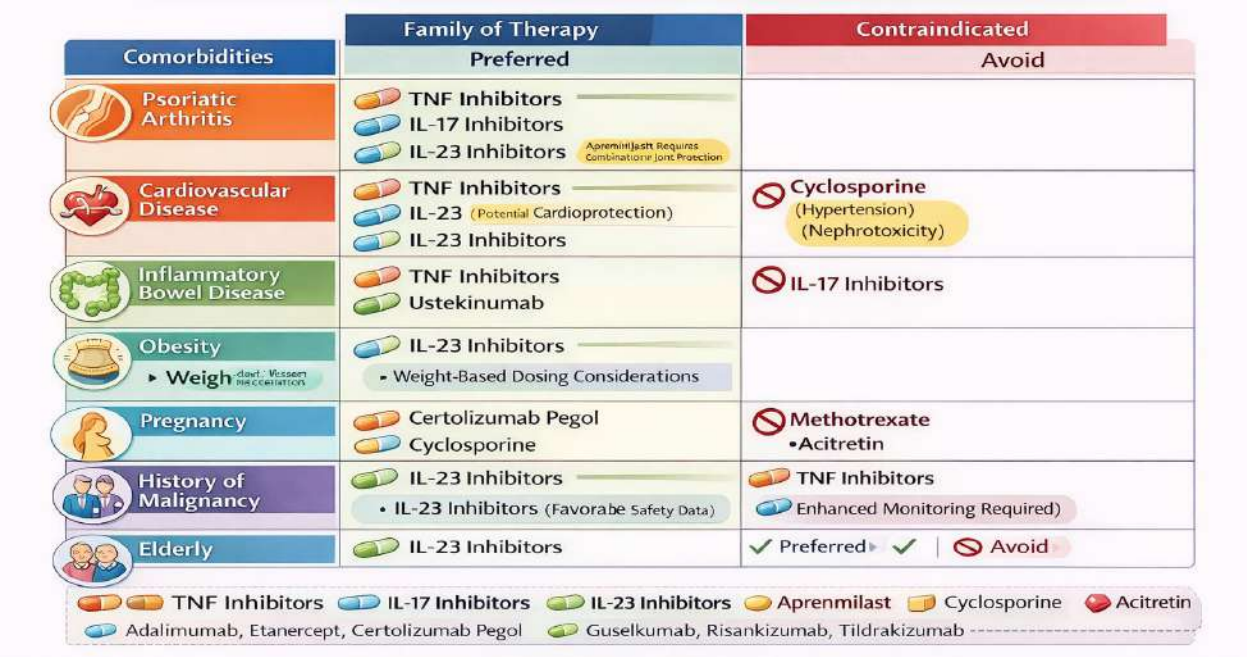

Figure 5: Treatment Selection Based on Comorbidities

For psoriatic arthritis, preferred agents include TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors; apremilast requires combination for joint protection. Cardiovascular disease favors TNF inhibitors with potential cardioprotection and IL-23 inhibitors with neutral profiles; cyclosporine is avoided due to hypertension and nephrotoxicity. Inflammatory bowel disease contraindicates IL-17 inhibitors; preferred options include TNF inhibitors and ustekinumab. Obesity requires weight-based dosing consideration, with IL-23 inhibitors showing preserved efficacy. Pregnancy prefers certolizumab pegol and cyclosporine; methotrexate and acitretin are contraindicated. Malignancy history supports IL-23 inhibitors with favorable safety data; TNF inhibitors require caution. Elderly patients benefit from IL-23 inhibitors given low infection risk; TNF inhibitors require enhanced monitoring.

13. Personalized Medicine and Biomarkers

13.1 The Promise of Precision Medicine in Psoriasis

The heterogeneity of psoriasis presentation, treatment response, and comorbidity risk supports the need for personalized approaches to therapy selection. Precision medicine aims to match specific treatments to individual patients based on genetic profiles, molecular signatures, and clinical characteristics, maximizing efficacy while minimizing adverse effects and costs.

The current "trial-and-error" approach to treatment selection results in delayed optimal therapy for many patients, with unnecessary exposure to ineffective agents and disease progression during inadequate treatment. Biomarker-guided therapy selection could identify patients likely to respond to specific agents, enabling first-line use of optimal therapy. The integration of multi-omics data including genomics, transcriptomics, proteomics, and metabolomics promises to define psoriasis

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endotypes with distinct therapeutic vulnerabilities (Tsoi et al., 2017).

13.2 Genetic Biomarkers for Treatment Response

Pharmacogenomic studies have identified genetic variants associated with treatment response. HLA-C*06:02 positivity predicts better response to ustekinumab and IL-17 inhibitors, potentially reflecting underlying disease biology more responsive to these targets. Variants in IL-23 pathway genes including *IL23R* polymorphisms influence response to IL-23 inhibitors, though effect sizes are modest.

TNF inhibitor pharmacogenomics reveals associations between *TNF* promoter variants and response, with some polymorphisms predicting better or worse outcomes. The development of antidrug antibodies, which reduces TNF inhibitor efficacy, shows genetic associations with HLA-DRB1 alleles. While these findings are not yet ready for clinical implementation, they demonstrate the feasibility of genetic prediction of treatment response and support ongoing biomarker development efforts (Capon et al., 2017).

13.3 Transcriptomic Signatures and Disease Endotypes

Transcriptomic analysis of psoriatic skin and blood identifies molecular subtypes with distinct pathogenic mechanisms. "IL-17 dominant" and "IFN-γ dominant" endotypes show differential responses to targeted therapies, with IL-17-high signatures predicting better response to IL-17 and IL-23 inhibitors. "Inflammatory" versus "proliferative" molecular profiles may indicate differential reliance on immune versus keratinocyte-intrinsic pathways.

Blood-based transcriptomic signatures offer non-invasive biomarker development. The psoriasis-related gene expression signature in peripheral blood correlates with skin disease activity and treatment response. Machine learning approaches integrating multiple transcriptomic features predict treatment response with increasing accuracy. Prospective validation of these signatures in clinical trials is necessary before implementation in routine practice (Li et al., 2014).

13.4 Proteomic and Metabolomic Biomarkers

Proteomic profiling identifies circulating proteins predictive of treatment response and comorbidity risk. IL-17 and IL-22 levels correlate with disease severity, while baseline levels may predict response to targeted therapies. Novel proteins including S100 family members, defensins, and angiogenic factors show promise as response biomarkers.

Metabolomic studies reveal alterations in lipid metabolism, amino acid pathways, and oxidative stress markers in psoriasis patients. Specific metabolic signatures may indicate insulin resistance, cardiovascular risk, or treatment response. The integration of metabolomic data with other omics layers provides comprehensive molecular characterization supporting precision medicine approaches (Armstrong et al., 2014).

13.5 Clinical Predictors of Response

Beyond molecular biomarkers, clinical features predict treatment response. Early age of onset, positive family history, and severe baseline disease predict better response to biologics. Obesity reduces response to fixed-dose biologics, while smoking cessation improves outcomes. Previous treatment history, particularly failure of multiple agents, predicts reduced response to subsequent therapies.

Psychological factors including depression and stress influence treatment adherence and response, supporting integrated biopsychosocial approaches. The presence of specific comorbidities guides treatment selection as discussed previously. These clinical predictors, while less precise than molecular biomarkers, are immediately available and should inform treatment decisions pending biomarker validation.

13.6 Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) measures biologic drug levels and antidrug antibodies to optimize dosing and guide switching decisions. Low drug levels with detectable antidrug antibodies indicate immunogenicity, supporting

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dose escalation or switch to an alternative agent. Low levels without antibodies suggest high drug clearance, potentially addressable by dose intensification or interval shortening.

TDM is established for TNF inhibitors in inflammatory bowel disease and rheumatoid arthritis, with emerging application in psoriasis. The availability of assays for IL-17 and IL-23 inhibitors enables similar optimization, though target levels and clinical utility require further definition. TDM-guided therapy may reduce unnecessary switching, identify non-adherence, and optimize treatment costs (Murdaca et al., 2020).

13.7 Future Directions: Clone-Directed Therapies

The identification of somatic mutations in psoriatic keratinocytes suggests potential for clone-directed therapies targeting specific genetic alterations. Mutations in *NOTCH1*, *TP53*, and other genes create neoplastic-like clones that may drive plaque persistence. Small molecule inhibitors targeting these specific mutations could eliminate pathogenic clones while sparing normal tissue.

This approach requires non-invasive methods to identify and monitor mutant clones, potentially through analysis of shed skin cells or circulating DNA. The development of topical or systemic agents selectively targeting mutant cells represents a long-term goal, potentially offering cure rather than management for selected patients. While currently experimental, clone-directed therapy exemplifies the potential for deep molecular understanding to transform treatment paradigms (Li et al., 2019).

14. Treatment Algorithms and Clinical Decision-Making

14.1 First-Line Therapy Selection

First-line therapy selection integrates disease severity, patient preferences, comorbidities, and healthcare system factors. For mild disease (PASI <10, BSA <10%), topical therapy with corticosteroids and vitamin D analogues remains appropriate, with calcineurin inhibitors for sensitive areas. Patient education regarding proper application technique and adherence support optimizes outcomes.

Moderate disease (PASI 10-20, BSA 10-20%) warrants escalation to phototherapy or systemic therapy based on patient factors. Phototherapy suits patients with accessible facilities, time availability, and preference for non-systemic approaches. Conventional systemic agents including methotrexate or apremilast are appropriate for patients with contraindications to biologics or limited access. Biologics should be considered for patients with significant quality of life impairment, psoriatic arthritis, or rapid control requirements.

Severe disease (PASI >20, BSA >20%) requires biologic therapy as first-line in most cases, given the superior efficacy and acceptable safety compared to conventional systemic agents. The choice among biologic classes considers comorbidities, speed of onset requirements, dosing preferences, and cost. IL-23 inhibitors offer the best balance of efficacy, safety, and convenience for many patients, though IL-17 inhibitors are preferred when rapid response is essential.

14.2 Treatment Escalation Strategies

Inadequate response to first-line therapy requires systematic evaluation before escalation. Assessment of adherence, application technique (for topicals), and dosing adequacy identifies modifiable factors. For biologics, measurement of drug levels and antidrug antibodies guides optimization versus switching. The treat-to-target approach defines specific timelines for reassessment, typically 12-16 weeks for systemic agents.

Escalation options depend on initial therapy. Topical failure may proceed to phototherapy, conventional systemic agents, or biologics. Conventional systemic agent failure supports transition to biologics, with selection based on mechanism of failure and patient factors. Biologic failure may involve intraclass switching (for immunogenicity or partial response), interclass switching (for primary non-response), or combination approaches. The availability of multiple agents within each class enables

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optimization of individual patient responses (Warren et al., 2020).

14.3 Managing Treatment Failure

True treatment failure, defined as inadequate response despite optimal dosing and adherence, requires reassessment of diagnosis, evaluation for confounding factors, and consideration of alternative or combination therapies. Diagnostic confirmation through biopsy may be warranted if atypical features suggest alternative diagnoses such as cutaneous T-cell lymphoma or pityriasis rubra pilaris.

Confounding factors including ongoing infections, medication non-adherence, psychological stress, and alcohol use may explain apparent treatment failure. Comorbidity optimization including weight reduction and smoking cessation improves response. For biologic failure, switching to an alternative mechanism typically produces better outcomes than cycling within the same class, though TNF inhibitor failures may respond to second TNF agents if the first was poorly tolerated rather than ineffective.

Refractory disease despite multiple biologic trials may warrant combination therapy, off-label interventions, or referral to specialized centers for clinical trial enrollment. The small subset of truly refractory patients highlights the need for continued therapeutic innovation.

14.4 Tapering and Discontinuation Considerations

Treatment discontinuation is appropriate for some patients achieving sustained remission, though relapse is common and often rapid. Gradual tapering of dosing frequency, rather than abrupt cessation, may prolong remission for some biologics. The decision to discontinue considers disease severity history, psychosocial impact of potential relapse, patient preference, and treatment access.

For conventional systemic agents, tapering reduces cumulative toxicity. Methotrexate may be tapered to weekly dosing or discontinued if sustained remission is achieved. Cyclosporine should be tapered due to rebound risk with abrupt cessation. Biologic tapering strategies are being evaluated in clinical trials, with some evidence supporting extended interval dosing for IL-23 inhibitors while maintaining response. Patient education regarding relapse recognition and prompt retreatment initiation is essential (Gisondi et al., 2015).

14.5 Long-Term Maintenance

Most patients with moderate-to-severe psoriasis require long-term maintenance therapy to sustain disease control and prevent comorbidity progression. The safety of continuous biologic therapy has been established through 5-year and longer follow-up studies, with sustained efficacy and no cumulative toxicity signals for IL-23 and IL-17 inhibitors. Monitoring for late adverse effects including malignancy and cardiovascular events continues through post-marketing surveillance.

Maintenance therapy should be periodically reassessed for continued necessity, with attempts at dose reduction or interval extension in stable patients. The integration of lifestyle modifications including weight management, smoking cessation, and stress reduction may enable reduced medication requirements. Patient support groups and educational resources promote adherence and optimal self-management.

14.6 Cost-Effectiveness Considerations

The high cost of biologic therapies necessitates consideration of cost-effectiveness in treatment selection. While biologics are expensive, their superior efficacy and impact on quality of life, work productivity, and comorbidity prevention may justify costs compared to less effective alternatives. Cost-effectiveness analyses generally favor IL-23 inhibitors and IL-17 inhibitors over TNF inhibitors when efficacy and safety are considered.

Access restrictions including step-editing requirements, prior authorization, and high patient cost-sharing limit optimal care for many patients. Advocacy for improved access, development of biosimilars, and value-based pricing models are necessary to ensure equitable care delivery. The cost-effectiveness of early aggressive intervention versus step-care approaches favors treat-to-target strategies when long-term outcomes are considered (Augustin et al., 2020).

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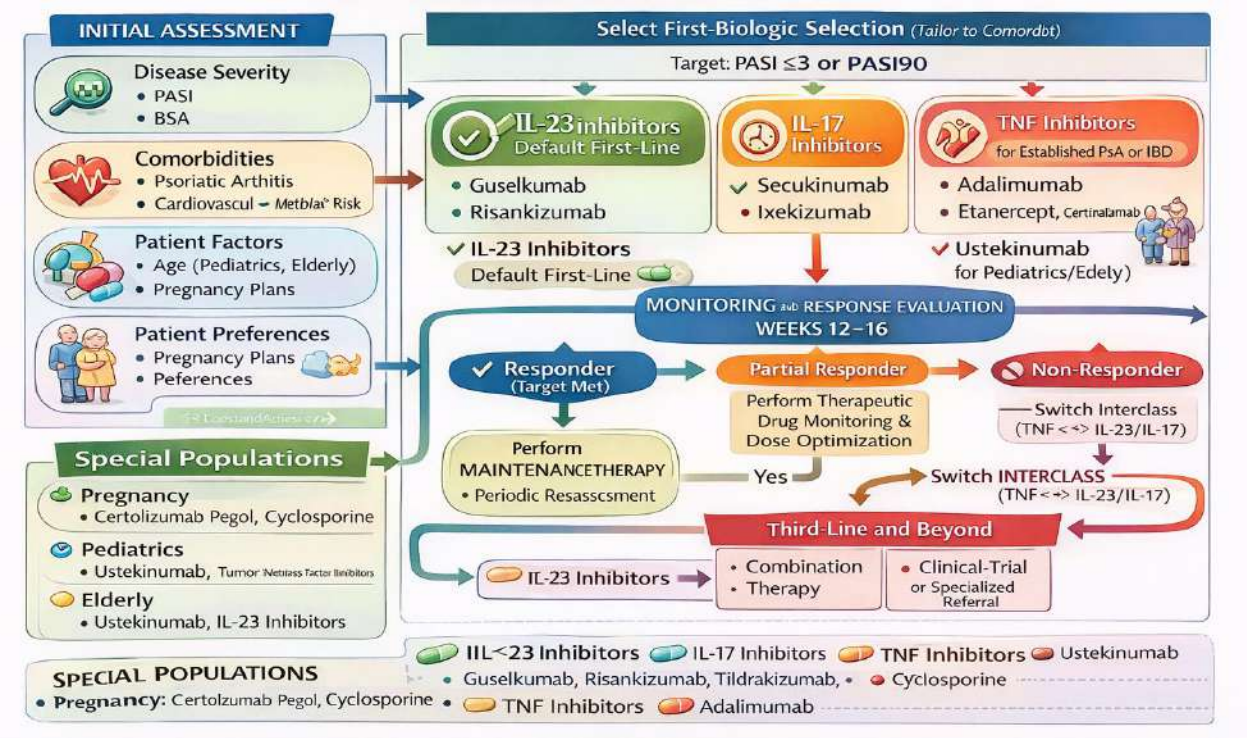

Figure 6: Comprehensive Treatment Algorithm for Moderate-to-Severe Psoriasis

Initial assessment includes disease severity (PASI, BSA, DLQI), comorbidity evaluation (PsA, cardiovascular risk, metabolic syndrome, IBD), and patient factors (age, pregnancy plans, preferences). First-line biologic selection considers comorbidities: IL-23 inhibitors (guselkumab, risankizumab, tildrakizumab) as default first-line given efficacy and safety; IL-17 inhibitors (secukinumab, ixekizumab) for rapid onset requirements; TNF inhibitors for established PsA or IBD; ustekinumab for pediatric or elderly patients. Monitoring occurs at weeks 12-16 with target PASI ≤3 or PASI90. Responders continue maintenance with periodic reassessment; partial responders undergo TDM and dose optimization; non-responders switch interclass. Second-line options include alternative IL-23/IL-17 agents or mechanism change based on failure mode. Third-line and beyond consider combination therapy, clinical trials, or specialized referral. Special populations (pregnancy, pediatrics, elderly) follow modified pathways.

15. Future Directions and Unmet Needs

15.1 Achieving Sustained Remission Versus "Cure"

The current therapeutic paradigm focuses on disease management rather than cure, with relapse following treatment discontinuation in most patients. The development of therapies achieving sustained remission or permanent disease modification represents the ultimate goal. Understanding the mechanisms of disease persistence including resident memory T-cells, epigenetic modifications, and somatic mutations may enable curative interventions.

Strategies to achieve cure may include combination approaches targeting multiple pathogenic pathways simultaneously, immune tolerance induction, or clone-directed elimination of pathogenic keratinocytes. The identification of patients achieving sustained remission after biologic discontinuation may reveal biomarkers predicting cure potential. Until curative therapies are developed, optimizing long-term disease control with minimal treatment burden remains the practical goal.

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15.2 Biomarker Development for Treatment Selection

The translation of biomarker research into clinical practice requires prospective validation in randomized trials. The development of point-of-care tests predicting treatment response would enable precision medicine approaches in routine clinical settings. Blood-based biomarkers are preferable to skin biopsies for patient acceptance and practicality.

Artificial intelligence and machine learning approaches integrating multi-omics data, clinical features, and treatment outcomes may identify non-obvious predictors of response. Collaborative networks pooling data from large patient cohorts are necessary to validate biomarkers across diverse populations. Regulatory pathways for biomarker-qualified therapies require development to support precision medicine implementation (Tsoi et al., 2017).

15.3 Long-Term Safety of Newer Agents

While short-term safety of IL-23 and IL-17 inhibitors is well-established, long-term data beyond 5 years remain limited. Post-marketing surveillance and registry studies must continue to detect rare adverse events and assess cumulative risks. Specific areas of interest include malignancy risk with long-term immunomodulation, cardiovascular outcomes, and effects on pregnancy outcomes.

The safety of novel agents including TYK2 inhibitors requires extensive post-marketing monitoring given the theoretical risks of broader immunosuppression. The development of standardized safety endpoints and international collaboration in pharmacovigilance will enhance the detection of safety signals and inform risk minimization strategies.

15.4 Optimal Treatment Sequencing

The optimal order of therapy selection to maximize long-term outcomes remains undefined. Network meta-analyses and head-to-head trials inform relative efficacy, but the best sequence for individual patients considering durability, safety, and cost requires further study. The concept of "induction of remission" followed by "maintenance" or "treatment holiday" strategies needs prospective evaluation.

The role of conventional systemic agents in the biologic era requires clarification, with potential utility as combination partners, bridging therapy, or alternatives in resource-limited settings. The integration of emerging oral small molecules into sequencing algorithms will depend on long-term safety and efficacy data compared to established biologics.

15.5 Combination Strategies for Refractory Disease

Patients failing multiple biologics represent a challenging population with significant unmet need. Rational combination approaches targeting complementary pathways may enhance efficacy, though safety considerations require careful evaluation. Biologic-biologic combinations, while effective in some studies, raise theoretical concerns about additive immunosuppression and infection risk.

Combinations of biologics with small molecules such as apremilast or deucravacitinib offer mechanistic synergy with potentially improved safety profiles. The development of fixed-dose combination products would improve convenience and adherence. Clinical trials in refractory populations with innovative designs including adaptive randomization and biomarker stratification are needed to define optimal combination strategies.

15.6 Access and Affordability Challenges

The disparity between therapeutic advances and global access represents a critical challenge. Biologics remain inaccessible to the majority of psoriasis patients worldwide due to cost and healthcare infrastructure limitations. The development of biosimilars, improved manufacturing technologies, and differential pricing models may improve access.

Topical and conventional systemic agents with established efficacy and safety retain important roles in resource-limited settings. The World Health Organization inclusion of essential medicines for psoriasis supports global access initiatives. Advocacy for psoriasis recognition as a

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serious non-communicable disease with significant disability is necessary to prioritize funding for treatment access programs (Danielsen et al., 2020).

15.7 Research Agenda Priorities

Future research priorities include the development of curative therapies, biomarker-guided precision medicine, and addressing health disparities. Basic research should focus on disease persistence mechanisms including resident memory T-cells, somatic mutations, and neuroimmune interactions. Translational research must validate biomarkers and develop point-of-care diagnostics.

Clinical trials should incorporate patient-reported outcomes, work productivity measures, and comorbidity endpoints beyond skin clearance. Real-world evidence from registries and administrative databases complements randomized trials in assessing long-term effectiveness and safety. Implementation science research optimizes the delivery of evidence-based care in diverse healthcare settings. The integration of patient advocacy in research prioritization ensures alignment with patient-centered outcomes (Gladman et al., 2021).

16. Conclusions

16.1 Summary of Key Findings

This comprehensive review has examined the current state of psoriasis understanding and management. Psoriasis is a chronic immune-mediated inflammatory disease affecting approximately 125 million people worldwide, with significant impact on quality of life and multiple associated comorbidities. The immunopathogenesis centers on the IL-23/Th17 axis, with genetic and environmental factors contributing to disease susceptibility and expression.

Treatment options have expanded dramatically, with biologic therapies targeting TNF-α, IL-12/23, IL-17, and IL-23 offering unprecedented efficacy in disease clearance. IL-23 inhibitors currently represent the optimal balance of efficacy, safety, and convenience for many patients with moderate-to-severe disease. Emerging therapies including TYK2 inhibitors, next-generation biologics, and microbiome-targeted approaches promise further improvements in outcomes.

16.2 The Evolving Therapeutic Landscape

The therapeutic landscape for psoriasis has transformed from symptomatic management with topical agents and phototherapy to precise immunomodulation with biologic and small molecule therapies. The treat-to-target paradigm emphasizes rapid achievement of complete or near-complete clearance, with treatment goals continually evolving as therapeutic capabilities advance. The availability of multiple highly effective agents enables individualized therapy selection based on patient characteristics, comorbidities, and preferences.

The pipeline of emerging therapies continues to expand, with oral agents challenging the dominance of injectable biologics and novel targets offering potential for refractory disease. The integration of personalized medicine approaches using biomarkers to guide treatment selection represents the next frontier in optimizing outcomes. However, access disparities between developed and developing regions remain a critical challenge requiring global health solutions.

16.3 Moving Toward Personalized, Patient-Centered Care

Optimal psoriasis management requires integration of clinical efficacy with patient values, quality of life considerations, and comorbidity management. Shared decision-making ensures that treatment choices align with individual patient goals and circumstances. The recognition of psoriasis as a systemic disease with cardiovascular, metabolic, and psychological comorbidities necessitates comprehensive, multidisciplinary care.

Patient-centered outcomes including work productivity, social participation, and sexual health should be assessed alongside objective disease measures. The stigma and psychological burden of visible skin disease require attention equal to physical symptoms. Supportive care including patient education, psychological support, and advocacy resources complements pharmacological therapy.

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16.4 Final Remarks on Improving Patient Outcomes

The future of psoriasis care holds promise for continued therapeutic advances, improved access, and ultimately disease cure. The convergence of basic immunology, genetics, and clinical research has created unprecedented opportunities to understand and treat this complex disease. Realization of these opportunities requires sustained research investment, global collaboration, and advocacy for patient access to optimal care.

The ultimate measure of success in psoriasis management extends beyond skin clearance to encompass overall health, quality of life, and social participation. As therapeutic options expand, the challenge shifts from disease control to disease prevention, comorbidity modification, and personalized care delivery. Meeting these challenges will require continued innovation, collaboration, and commitment to the millions of patients worldwide living with psoriasis.

17. Conflict of Interest Statement

All authors have no conflict of interest.

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