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Review Article

A REVIEW ARTICLE ON PSORIASIS VULGARIS**S. Shaheena Begum, PG. Pujitha Yadav**

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Abstract:

Psoriasis is a complex chronic inflammatory skin disease caused by the dynamic interplay between multiple genetic risk foci, environmental risk factors, and excessive immunological abnormalities. Psoriasis affects approximately 2% of the population worldwide, and dramatic advances have been achieved in the understanding and treatment options for psoriasis. Recent progress in biological therapies has revealed the fundamental roles of tumor necrosis factor- α , interleukin (IL)-23p19, and the IL-17A axis together with skin-resident immune cells and major signal transduction pathways in the pathogenesis of psoriasis.

In addition to IL-17-producing T helper17 cells, innate lymphoid cell (ILC)3 induces psoriasis rashes directly without T-cell/antigen interaction in response to the released antimicrobial peptides from activated keratinocytes and inflammatory cytokines.

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INTRODUCTION:

Psoriasis is a lifelong immune-mediated inflammatory skin disease, associated with morbidities such as psoriatic arthropathy, psychological, cardiovascular and hepatic diseases. In 2014, the World Health Organization recognised psoriasis as a serious non-communicable disease and highlighted the distress related to misdiagnosis, inadequate treatment and stigmatisation of this disease. The Global Burden of Disease Study estimated that psoriasis accounted for 5.6 million all-age disability-adjusted life-years (DALYs) in 2016; at least three-fold that of inflammatory bowel disease.

Psoriasis is a chronic proliferative and inflammatory condition of the skin. It is characterized by erythematous plaques covered with silvery scales, particularly over the extensor surfaces, scalp, and lumbosacral region. The disorder can also affect the joints and eyes. Psoriasis has no cure and the disease waxes and wanes with flareups. Many patients with psoriasis develop depression as the quality of life is poor. There are several subtypes of psoriasis but the plaque type is the most common and presents on the trunk, extremities, and scalp. Close examination of the plaques usually reveals white silvery scales. The eye is involved in about 10% of patients, mostly women. In general, the eye is rarely involved alone; it is almost always associated with skin features.

DEFINITION

It is a chronic, non-infectious skin inflammation involving keratin synthesis that results in psoriatic patches.

It is an inflammatory skin disease in which the skin cell replicate at an extremely rapid rate. New cells are produced 8 times faster than normal but the rate at which old cells sloughed off is unchanged, this causes the cell build up on skin surface, forming thick patches or plaques of red sores, covered with flaky, silvery white dead skin cells (scale).

EPIDEMIOLOGY

Psoriasis is a chronic inflammatory skin disease with a strong genetic predisposition and autoimmune pathogenic traits. The worldwide prevalence is about 2%, but varies according to regions. It shows a lower prevalence in Asian and some African populations, and up to 11% in Caucasian and Scandinavian populations.

- a. Clinical Classification
- b. Psoriasis Vulgaris
- c. Inverse Psoriasis
- d. Guttate Psoriasis
- e. Pustular psoriasis
- f. Comorbidities in Psoriasis

Clinical Classification

The dermatologic manifestations of psoriasis are varied; psoriasis vulgaris is also called plaque-type psoriasis, and is the most prevalent type. The terms psoriasis and psoriasis vulgaris are used interchangeably in the scientific literature; nonetheless, there are important distinctions among the different clinical subtypes (See [Figure 1](#)).

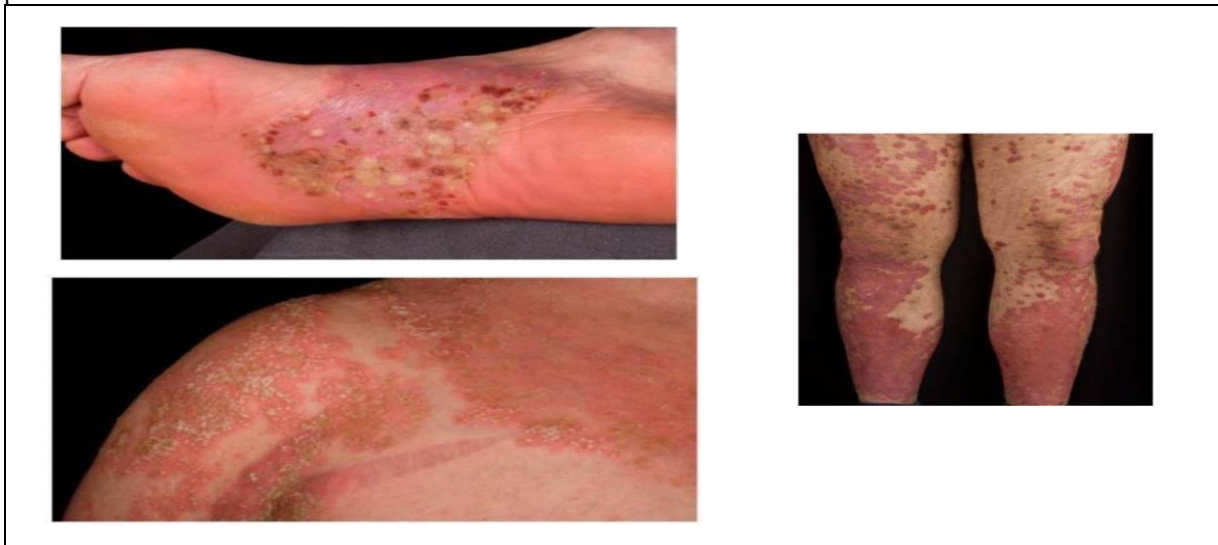


Figure 1

Psoriasis Vulgaris

About 90% of psoriasis cases correspond to chronic plaque-type psoriasis. The classical clinical manifestations are sharply demarcated, erythematous, pruritic plaques covered in silvery scales. The plaques can coalesce and cover large areas of skin. Common locations include the trunk, the extensor surfaces of the limbs, and the scalp

Inverse Psoriasis

Also called flexural psoriasis, inverse psoriasis affects intertriginous locations, and is characterized clinically by slightly erosive erythematous plaques and patches.

Guttate Psoriasis

Guttate psoriasis is a variant with an acute onset of small erythematous plaques. It usually affects children or adolescents, and is often triggered by group-A streptococcal infections of tonsils. About one-third of patients with guttate psoriasis will develop plaque psoriasis throughout their adult life.

Pustular Psoriasis

Pustular psoriasis is characterized by multiple, coalescing sterile pustules. Pustular psoriasis can be localized or generalized. Two distinct localized phenotypes have been described: psoriasis pustulosa palmoplantaris (PPP) and acrodermatitis continua of Hallopeau. Both of them affect the hands and feet; PPP is restricted to the palms and soles, and ACS is more distally located at the tips of fingers and toes, and affects the nail apparatus. Generalized pustular psoriasis presents with an acute and rapidly progressive course characterized by diffuse redness and subcorneal pustules, and is often accompanied by systemic symptoms. *Erythrodermic psoriasis* is an acute condition in which over 90% of the total body surface is erythematous and inflamed. Erythroderma can develop on any kind of psoriasis type, and requires emergency treatment ([Figure 2](#)).

Comorbidities In Psoriasis

Psoriasis typically affects the skin, but may also affect the joints, and has been associated with a number of diseases. Inflammation is not limited to the psoriatic

skin, and has been shown to affect different organ systems. Thus, it has been postulated that psoriasis is a systemic entity rather than a solely dermatological disease. When compared to control subjects, psoriasis patients exhibit increased hyperlipidemia, hypertension, coronary artery disease, type 2 diabetes, and increased body mass index. The metabolic syndrome, which comprises the aforementioned conditions in a single patient, was two times more frequent in psoriasis patients. Coronary plaques are also twice as common in

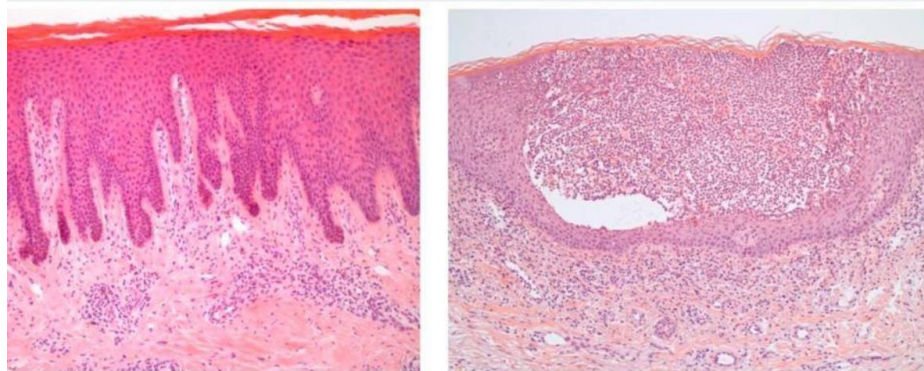
psoriasis patients when compared to control subjects. Several large studies have shown a higher prevalence of diabetes and cardiovascular disease correlating with the severity of psoriasis. There are divided opinions regarding the contribution of psoriasis as an independent cardiovascular risk factor; however, the collective evidence supports that psoriasis independently increases risk for myocardial infarction, stroke, and death due to cardiovascular disease (CVD). In addition, the risk was found to apply also to patients with mild psoriasis to a lower extent. Vascular inflammation assessed via ¹⁸F-fluorodeoxyglucose positron emission tomography-computed tomography (¹⁸F-FDG PET/CT) found psoriasis duration to be a negative predicting factor. It was suggested that the cumulative effects of low-grade chronic inflammation might accelerate vascular disease development. In a study by Metha et al., systemic and vascular inflammation in six patients with moderate to severe psoriasis was quantified by FDG-PET/CT. Inflammation foci were registered as expected in the skin, joints, and tendons. In addition, FDG uptake in the liver and aorta revealed subclinical systemic inflammation. Furthermore, standardized uptake values were reduced in the liver, spleen, and aorta following treatment with ustekinumab {Kim, 2018 #359}. A new biomarker to assess CVD risk in psoriasis patients was proposed by nuclear magnetic resonance spectroscopy.





PATHOGENESIS

The hallmark of psoriasis is sustained inflammation that leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation. The histology of the psoriatic plaque shows acanthosis (epidermal hyperplasia), which overlies inflammatory infiltrates composed of dermal dendritic cells, macrophages, T cells, and neutrophils. Neovascularization is also a prominent feature. The inflammatory pathways active in plaque psoriasis and the rest of the clinical variants overlap, but also display discrete differences that account for the different phenotype and treatment outcomes.



- i. Main Cytokines and Cell Types in Plaque Psoriasis
 - ii. Pathophysiology in Variants
 - iii. Autoimmunity in Psoriasis
 - iv. Genetics
 - a. Antigen Presentation
 - b. Genetic Variants Implicated in Aberrant Keratinocyte Proliferation and Differentiation
 - v. Epigenetics
 - vi. Microbiome
- Main Cytokines And Cell Types In Plaque Psoriasis**

Disturbances in the innate and adaptive cutaneous immune responses are responsible for the development and sustainment of psoriatic inflammation. An activation of the innate immune

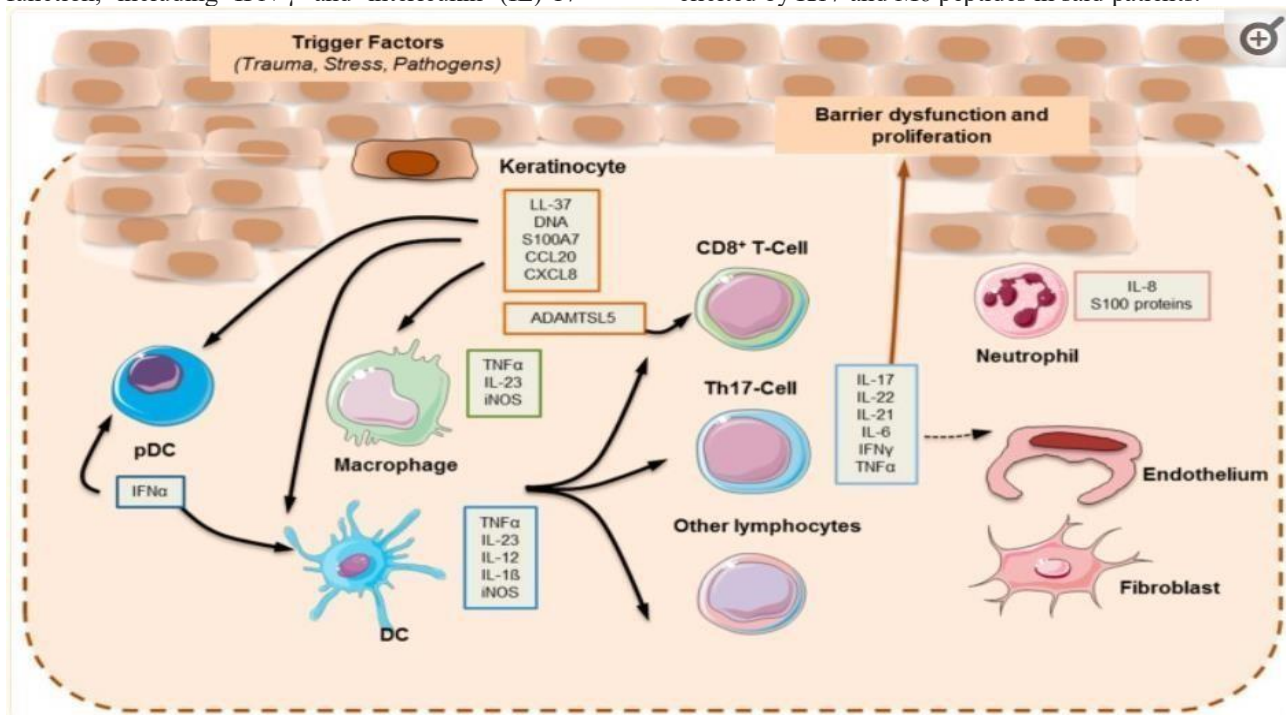
system driven by endogenous danger signals and cytokines characteristically coexists with an autoinflammatory perpetuation in some patients, and T cell-driven autoimmune reactions in others. Thus, psoriasis shows traits of an autoimmune disease on an (auto)inflammatory background, with both mechanisms overlapping and even potentiating one another. The main clinical findings in psoriasis are evident at the outermost layer of the skin, which is made up of keratinocytes. However, the development of the psoriatic plaque is not restricted to inflammation in the epidermal layer, but rather is shaped by the interaction of keratinocytes with many different cell types (innate and adaptive immune cells,

vasculature) spanning the dermal layer of the skin. The pathogenesis of psoriasis can be conceptualized into an initiation phase possibly triggered by trauma (Koebner phenomenon), infection, or drugs and a maintenance phase characterized by a chronic clinical progression (see [Figure 5](#)). It is well known that dendritic cells play a major role in the initial stages of disease. Dendritic cells are professional antigen-presenting cells. However, their activation in psoriasis is not entirely clear. One of the proposed mechanisms involves the recognition of antimicrobial peptides (AMPs), which are secreted by keratinocytes in response to injury and are characteristically overexpressed in psoriatic skin. Among the most studied psoriasis-associated AMPs are LL37, β defensins, and S100 proteins. LL37 or cathelicidin has been attributed a pathogenic role in psoriasis. It is released by damaged keratinocytes, and subsequently forms complexes with self-genetic material from other damaged cells. LL37 bound to DNA stimulates toll-like receptor (TLR) 9 in plasmacytoid dendritic cells (pDCs). The activation of pDC is key in starting the development of the psoriatic plaque, and is characterized by the production of type I IFN (IFN- α and IFN- β). Type I IFN signaling promotes myeloid dendritic cells (mDC) phenotypic maturation, and has been implicated in Th1 and Th17 differentiation and function, including IFN- γ and interleukin (IL)-17

production, respectively. Whilst LL37–DNA complexes stimulate pDCs through TLR9, LL37 bound to RNA stimulates pDCs through TLR7. In addition, LL37–RNA complexes act on mDCs via TLR8. Activated mDCs migrate into draining lymph nodes and secrete tumor necrosis factor (TNF)- α , IL-23, and IL-12, with the latter two modulating the differentiation and proliferation of Th17 and Th1 cell subsets, respectively. Furthermore, slan⁺ monocytes, which are important pro-inflammatory cells found in psoriasis skin lesions, respond to LL37–RNA activation by secreting high amounts of TNF- α , IL-12, and IL-23.

Pathophysiology In Variants

Whereas the TNF α –IL23–Th17 axis plays a central role in T cell-mediated plaque psoriasis, the innate immune system appears to play a more prominent role in the pustular variants of psoriasis. Different pathomechanisms are associated with distinct psoriasis subtypes. In guttate psoriasis, streptococcal superantigens are thought to stimulate the expansion of T cells in the skin. It was shown that there is a considerable sequence homology between streptococcal M proteins and human keratin 17 proteins. Molecular mimicry may play a role in patients with the major histocompatibility HLACw6 allele, since CD8(+) T cell IFN- γ responses were elicited by K17 and M6 peptides in said patients.



Pustular psoriasis is characterized by the increased expression of IL-1 β , IL-36 α , and IL-36 γ transcripts, which have been found in pustular psoriasis compared to psoriasis vulgaris. Nevertheless, IL-17 signaling is also involved in pustular psoriasis and patients with generalized pustular psoriasis without IL-36R mutations responded to anti-IL-17 treatments. In nail psoriasis and psoriatic arthritis (PsA), an increased expression of TNF- α , NF κ B, IL-6, and IL-8 in psoriasis-affected nails is consistent with the inflammatory markers found on lesional psoriatic skin. The pathophysiology of PsA and psoriasis is shared as synovial tissue in psoriatic arthritis expresses pro-inflammatory cytokines: IL-1, IFN- γ , and TNF α . Infiltrating cells in psoriasis arthritis, tissues, and synovial fluid revealed large clonal expansions of CD8⁺ T cells. Joint pathology, specifically bone destruction, is partly mediated via IL-17A signaling, which induces the receptor activator of nuclear factor kappa b ligand (RANKL), and in turn activating osteoclasts. Pro-inflammatory cytokines IL-1 β and TNF- α act in synergy with the local milieu.

Autoimmunity In Psoriasis

Psoriasis shows clear autoimmune-related pathomechanisms. This very important area of research will allow for a deeper understanding of to which extent autoantigen-specific T cells contribute to the development, chronification, and overall course of the disease. LL37 is one of two well-studied T cell autoantigens in psoriasis. CD4⁺ and CD8⁺ T cells specific for LL37 were found in two-thirds of patients with moderate to severe plaque psoriasis in a study. LL37-specific T cells produce IFN γ , and CD4⁺ T cells produce IL-17, IL-21, and IL-22 as well. LL37-specific T cells can be found in lesional skin or in the blood, where they correlate with disease activity. CD8⁺ T cells activated through LL37 engage in epidermotropism, autoantigen recognition, and the further secretion of Th17 cytokines. The melanocytic protein ADAMTSL5 was found to be an HLA-C*06:02-restricted autoantigen recognized by an autoreactive CD8⁺ T cell TCR. This finding establishes melanocytes as autoimmune target cells, but does not exclude other cellular targets. Other autoantigen candidates include lipid antigens generated by phospholipase A2 (PLA2) group IVD (PLA2G4D) and hair follicle-derived keratin 17. Interestingly, keratin 17 exposure only lead to CD8⁺ T cell proliferation in patients with the HLA-Cw*0602 allele (see above).

Genetics

Psoriasis has a genetic component that is supported by patterns of familial aggregation. First and second-degree relatives of psoriasis patients have an increased incidence of developing psoriasis, while monozygotic twins have a two to threefold increased risk compared to dizygotic twins. Determining the precise effect of genetics in shaping innate and adaptive immune responses has proven problematic for psoriasis and other numerous immune-mediated diseases. The genetic variants associated with psoriasis are involved in different biological processes, including immune functions such as antigen presentation, inflammation, and keratinocyte biology.

Antigen Presentation

Genome-wide linkage studies of psoriasis-affected families have so far detected at least 60 chromosomal loci linked to psoriatic susceptibility ; the most prominent locus is PSORS1, which has been attributed up to 50% of the heritability of the disease. PSORS1 is located on chromosome 6p21 within the major histocompatibility complex (MHC), which is specifically in the class I telomeric region of HLA-B, and spans an approximately 220 kb-long segment and corresponds to HLA-Cw6 (C*06:02). HLA-Cw6 is strongly linked to early and acute onset psoriasis. The results of numerous genome-wide association studies (GWAS) in psoriasis are consistent with the prominent role of PSORS1 as a risk factor, but have also revealed over 50 single-nucleotide polymorphisms (SNPs) to be associated to psoriasis Variants involving the adaptive and immune system are a constant result in these studies.

Genetic Variants Implicated In Aberrant Keratinocyte Proliferation And Differentiation

The immunogenetics of IL-23 are strongly associated with psoriasis. IL-23 is a dimer composed of a specific subunit, p19, and a p40 subunit, which is shared with IL-12. IL-23 signals through a heterodimeric receptor expressed by both innate and adaptive immune cells, which include Th17, natural killer T, $\gamma\delta$ T cells, and ROR γ t⁺ innate lymphoid cells. The IL-23R signals through JAK2/TYK2 and STAT3. SNPs in the regions coding for the IL-23 cytokine (both the p40 and p19 subunit) as well as the IL-23R have been identified to convey psoriasis risk. Furthermore, these variants have been found to be associated with Crohn's disease, psoriatic arthritis, and ankylosing spondylitis. IL-23 drives the expansion of Th17 T cells that produce IL-17A/F, which is another set of cytokines whose role is pivotal in the pathogenesis of psoriasis.

Monoclonal antibodies targeting both the common p40 and the specific p19 subunit of IL-23 have proven to have high clinical efficacy. As mentioned above, STAT3 is found in downstream signaling by IL-23, and is therefore essential in T cell development and Th17 polarization. STAT3 has also been detected in psoriasis GWAS, and its variants are associated with psoriasis risk. Furthermore, transcription factor Runx1 induces Th17 differentiation by interacting with ROR γ t. Interestingly, the interaction of Runx1 with Foxp3 results in reduced IL-17 expression. *CARD14* mapping was shown to correspond to PSORS2. The CARD family encompasses scaffolding proteins that activate NF- κ B. It was suggested that in psoriasis patients with respective *CARD14* mutations, a triggering event can result in an aberrant NF κ B over activation. *CARD14* is expressed in keratinocytes and in psoriatic skin; it is upregulated in the suprabasal epidermal layers and downregulated in the basal layers. In healthy skin, *CARD14* is mainly localized in the basal layer. Mutations in *CARD14* have been shown to be associated with psoriasis, as well as with familial pityriasis rubra pilaris (PRP). The NF- κ B signaling pathway is involved in the production of both IL-17 and TNF- α , and thus participates in adaptive and innate immune responses; it is upregulated in psoriatic lesions and is responsive to treatment. Gene variations in *NFKB1A*, *TNIP1*, and *TRAF3PI2* affecting NF- κ B regulatory proteins have been linked to psoriasis via GWAS. TRAF3PI2 codes for the ACT1 adaptor protein and the specific variant TRAF3IP2 p. Asp10Asn was associated to both psoriasis and psoriatic arthritis. The different clinical psoriasis variants may have additional genetic modifiers. For instance, mutations in the antagonist to the IL-36 receptor (IL-36RN), belonging to the IL-1 pro-inflammatory cytokine family, have been linked to pustular psoriasis. Recessive mutations in *IL36RN*, coding for the IL-36 receptor antagonist, have been associated with generalized pustular psoriasis (GPP). This mutation is also found in palmar plantar pustulosis and acrodermatitis continua of Hallopeau. Furthermore, in patients with preexisting plaque-type psoriasis, the gain of function mutation in *CARD14*, p.Asp176His, was found to be a predisposing factor for developing GPP.

Epigenetics

The quest for the missing heritability associated with psoriasis candidate genes has fueled the search for epigenetic modifications. Epigenetic mechanisms modify gene expression without changing the genomic sequence; some examples include: long

noncoding RNA (lncRNA), microRNA (miRNA) silencing, and cytosine and guanine (CpG) methylation. lncRNA are at least 200 nucleotides long, and are not transcribed to protein. At least 971 lncRNAs have been found to be differentially expressed in psoriatic plaques compared to normal skin. Thereof, three differentially expressed lncRNAs in proximity to known psoriasis susceptibility loci at *CARD14*, *LCE3B/LCE3C*, and *IL23R*, and are thought to modulate their function. miRNAs are small, evolutionarily conserved, noncoding RNAs that base pair with complementary sequences within mRNA molecules, and regulate gene expression at the posttranscriptional level, usually downregulating expression. Most of the studies of miRNAs in association with psoriasis address the plaque-type variant (see [Table 1](#)), and so far, more than 250 miRNAs are aberrantly expressed in psoriatic skin. A prominent role has been attributed to miR-31, which is upregulated in psoriatic skin and regulates NF- κ B signaling as well as the leukocyteattracting and endothelial cell-activating signals produced by keratinocytes. miR-21 is an oncomiR with a role in inflammation, and has been found to be elevated in psoriatic skin. Increased miR-21 has been localized not only to the epidermis, but is also found in the dermal inflammatory infiltrates, and correlates with elevated TNF- α mRNA expression. miR-221 and miR-222 are among other upregulated miRNAs in psoriatic skin. The aberrant expression of miR-21, miR-221, and miR-222 correlates with a downregulation of the tissue inhibitor of metalloprotease 3 (TIMP3). TIMP3 is a member of the matrix metalloprotease family with a wide range of functions. Increased levels of said miRs are thought to result in unopposed matrix metalloprotease activity, leading to inflammation (partly via TNF- α -mediated signaling) and epidermal proliferation. miR-210 was found to be highly expressed in psoriasis patients, and induced Th17 and Th1 differentiation while inhibiting Th2 differentiation through STAT6 and LYN repression. Serum levels of miR-33, miR-126, and miR-143, among others, have been proposed as potential biomarkers of disease. However, the studies have so far failed to consistently present elevations of a single miRNA in psoriatic patients. Thus, alterations of miRNA expression are better interpreted in the context of miRNA profiles, which have been reported to shift following psoriasis treatments. Thus, miRNA expression profiles could potentially be used to predict response to treatment and personalize therapies.

Table 1

MicroRNAs (miRNAs) increased in psoriasis.

miRNA	Target Genes	Tissue/Cell Type (Human)	Function
miR-21	<i>TIMP3, TPM1, PDCD4, PTEN, IL12A, RECK, RTN4, NFIB</i>	Skin, PBMCs	Keratinocyte differentiation and proliferation, T cell activation, inflammation [136]
miR-31	<i>FIH-1, STK40</i>	Skin	NF-κB activity, keratinocyte differentiation and proliferation [135]
miR-135b	<i>COL4A3</i>	Skin	Keratinocyte differentiation and proliferation [137]
miR-146a	<i>IRAK1, TRAF6, EGFR</i>	Skin	Hematopoiesis, inflammation, and keratinocyte proliferation [142,143]
miR-155	<i>CTLA-4</i>	Skin	Inflammation [144]
miR-203	<i>TNF-α, IL-8, IL-24, SOCS-3, SOCS-6</i>	Skin	STAT3 signaling, keratinocyte differentiation and proliferation, and inflammation [145]
miR-210	<i>FOXP3</i>	PBMCs	Regulatory T cell activation Induction of Th17 and Th1 differentiation [139,146]
miR-221/222	<i>TIMP3, c-KIT</i>	Skin	Immune cell activation Keratinocyte proliferation [138]
miR-424	<i>MEK1, Cyclin E1</i>	Skin	Keratinocyte differentiation and proliferation [147]

Microbiome

The skin microbiome exerts an active role in immune regulation and pathogen defense by stimulating the production of antibacterial peptides and through biofilm formation. A differential colonizing microbiota in comparison to healthy skin has been found in several dermatologic diseases, including atopic dermatitis, psoriasis, and acne vulgaris. It is hypothesized that an aberrant immune activation triggered by skin microbiota is involved in the pathogenesis of autoimmune diseases. For instance, there is growing evidence that the steady-state microbiome plays a role in autoimmune diseases such as in inflammatory bowel disease. The overall microbial diversity is increased in the psoriatic plaque. However, an increase in Firmicutes and Actinobacteria phyla were found in psoriatic plaques (Table 2). Proteobacteria were found to be higher in healthy skin when compared to psoriatic patients.

Nevertheless, Proteobacteria were found to be increased in the trunk skin biopsies of psoriatic lesions.

A combined increase in *Corynebacterium*, *Propionibacterium*, *Staphylococcus*, and *Streptococcus* was found in psoriatic skin; however, in another study, *Staphylococci* were significantly lower in psoriatic skin compared to healthy controls. Certain fungi such as *Malassezia* and *Candida albicans*, and viruses such as the human papilloma virus have been associated with psoriasis. So far, *Malassezia* proved to be the most abundant fungus in psoriatic and healthy skin. Nevertheless, the colonization level of *Malassezia* in psoriasis patients was lower than that in healthy controls. Further studies are required to explain the role of the microbiome signature and the dynamics among different commensal and pathogenic phyla.

Table 2

Psoriasis microbiome. † increased. > higher than.

Study	Sample (n)	Method	Psoriasis	Healthy Skin	Comments
Gao et al., 2008 [153]	Skin swabs (six psoriatic patients)	broad range PCR	↑ diversity ↑ Firmicutes	↑ Actinobacteria ↑ Proteobacteria	Healthy controls taken from previous study [158].
Alekseyenko et al., 2013 [154]	Skin swabs (54 psoriasis patients, 37 controls)	High-throughput 16S rRNA gene sequencing	↑ Actinobacteria/Firmicutes ↑ Corynebacterium, Propionibacterium, Staphylococcus, Streptococcus ↑ Corynebacterium, Streptococcus, Staphylococcus	↑ Proteobacteria	OTUs Acidobacteria and Schlegella were strongly associated with psoriasis status. Samples were site-matched.
Fahlen et al., 2012 [151]	Skin biopsies (10 psoriasis patients, 10 healthy controls)	Pyrosequencing targeting the V3-V4 regions of the 16S rRNA gene	Streptococcus > Staphylococcus ↑ Proteobacteria (trunk skin) ↑ Propionibacteria/Staph. (limb skin)	↑ Actinobacteria	Included dermis and adnexal structures. Bacterial diversity was increased in the control group (unmatched sites), but not statistically significant. Firmicutes, Proteobacteria, and Actinobacteria predominant in healthy and psoriatic skin.
Takemoto et al., 2015 [156]	Psoriatic scale samples (12 psoriatic patients, 12 healthy controls)	Pyrosequencing for fungal rRNA gene sequences	↑ fungal diversity ↓ Malassezia	↑ Malassezia	Fungal microbiome study Malassezia were the most abundant species in psoriatic and healthy skin.

THERAPY

Psoriasis is a chronic relapsing disease, which often necessitates a long-term therapy. The choice of therapy for psoriasis is determined by disease severity, comorbidities, and access to health care. Psoriatic patients are frequently categorized into two groups: mild or moderate to severe psoriasis, depending on the clinical severity of the lesions, the percentage of affected body surface area, and patient quality of life. Clinical disease severity and response to treatment can be graded through a number of different scores. The PASI score has been extensively used in clinical trials, especially those pertaining to the development of the biologic drugs, and will be used throughout this review. Mild to moderate psoriasis can be treated topically with a combination of glucocorticoids, vitamin D analogues, and phototherapy. Moderate to severe psoriasis often requires systemic treatment. The presence of comorbidities such as psoriasis arthritis is also highly relevant in treatment selection. In this review, we will address the systemic therapies as small-molecule (traditional and new) and biologic drugs. A number of case reports and case series have suggested that tonsillectomy has a therapeutic effect in patients with guttate psoriasis and plaque psoriasis. A systematic review concluded that the evidence is insufficient to make general therapeutic recommendations for tonsillectomy, except for selected patients with recalcitrant psoriasis, which is clearly associated to tonsillitis. A recent study stated that HLA-Cw*0602 homozygosity in patients with plaque psoriasis may predict a favorable outcome to tonsillectomy. To date, a single randomized, controlled clinical trial showed that tonsillectomy produced a significant

improvement in patients with plaque psoriasis in a two-year follow-up timespan. Furthermore, the same cohort was evaluated to assess the impact of the clinical improvement after tonsillectomy on quality of life. The study reported a 50% improvement in health-related quality of life, and a mean 59% improvement in psoriasis-induced stress. Tonsillectomy was considered worthwhile by 87% of patients who underwent the procedure .

i. Small-Molecule Therapies ii. Biologics

TNF- α

IL23/Th17 axis

Biosimilars in Psoriasis

Drugs in the Research Pipeline

Small-Molecule Therapies

In the past years, an accelerated development in psoriasis therapies has resulted in advanced targeted biological drugs. Methotrexate (MTX), cyclosporin A, and retinoids are traditional systemic treatment options for psoriasis. All of the former are oral drugs with the exception of MTX, which is also available for subcutaneous administration. They will be briefly discussed in this review (see [Table 3](#)). The section ends with an overview on dimethyl fumarate and apremilast, which are newer drugs that have been approved for psoriasis.

MTX is a folic acid analogue that inhibits DNA synthesis by blocking thymidine and purine biosynthesis. The initial recommended dose of 7.5–10 mg/weekly may be increased to a maximum of 25 mg/weekly. A recent retrospective study reported successful treatment response (defined by PASI decrease of 50% to 75% and absolute DLQI value) was reached by 33%, 47%, and 64% of patients at

three, six, and 12 months, respectively. There is conflicting evidence regarding MTX effectiveness on psoriatic arthritis.

Table 3

Drugs available for psoriasis therapy.

Drug	Mechanism	Application
Methotrexate	Dihydrofolate reductase inhibition blocks purine biosynthesis; induction of lymphocyte apoptosis	s.c./oral
Cyclosporin	Calcineurin inhibition leading to reduced IL-2	Oral
Acitretin	Normalization of keratinocyte proliferation/differentiation through retinoid receptor binding	Oral
Fumarate	Intracellular glutathione, modulation of Nrf2, NF- κ B, and HIF-1 α ; promoting a shift from a pro-inflammatory Th1/Th17 response to an anti-inflammatory/regulatory Th2 response.	Oral
Apremilast	PDE4 inhibitor increases intracellular cAMP levels in immune and non-immune cell types modulating inflammation	Oral
Etanercept	Dimeric human fusion protein mimicking TNF- α R	s.c.
Infliximab	Chimeric IgG1 κ monoclonal antibody that binds to soluble and transmembrane forms of TNF- α	i.v.
Adalimumab	Human monoclonal antibody against TNF- α	s.c.
Certolizumab	Fab portion of humanized monoclonal antibody against TNF- α conjugated to polyethylene glycol	s.c.
Ustekinumab	Human IgG1 κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the interleukin (IL)-12 and IL-23 cytokines IL-12/IL-23 p40	s.c.
Tildrakizumab	Humanized IgG1 κ , which selectively blocks IL-23 by binding to its p19 subunit	s.c.
Guselkumab	Human immunoglobulin G1 lambda (IgG1 λ) monoclonal antibody that selectively blocks IL-23 by binding to its p19 subunit	s.c.
Risankizumab	Humanized IgG1 monoclonal antibody that inhibits interleukin-23 by specifically targeting the p19 subunit	s.c.
Secukinumab	Human IgG1 κ monoclonal antibody against IL-17A	s.c.
Ixekizumab	Humanized, immunoglobulin G4 κ monoclonal antibody selectively binds and neutralizes IL-17A	s.c.
Brodalumab	Human monoclonal IgG2 antibody directed at the IL-17RA	s.c.

A recent publication reported 22.4% of patients achieved minimal arthritic disease activity, and 27.2% reached a PASI 75 at week 12. Furthermore, HLA-Cw6 has been suggested as a potential marker for patients who may benefit from MTX treatment. The most common side effects include nausea, leucopenia, and liver transaminase elevation. Despite the potential side effects and its teratotoxicity, it remains a frequently used cost-effective first-line drug, and the close monitoring of liver function and full blood count make a long-term administration feasible. Cyclosporine is a T cell-inhibiting immunosuppressant from the group of the calcineurin inhibitors. Cyclosporine is effective as a remission inducer in psoriasis and as maintenance therapy for up to two years. Hypertension, renal toxicity, and non-melanoma skin cancer are significant potential side effects. Nephrotoxicity is related to the duration of treatment and the dose. Cyclosporine is employed as an intermittent short-term therapy. The dosage is 2.5 to 5.0 mg/kg of body weight for up to 10 to 16 weeks.

Tapering of the drug is recommended to prevent relapse.

Biologics

In the context of psoriasis treatment, current use of the term *biologics* refers to complex engineered molecules including monoclonal antibodies and receptor fusion proteins. Biologics are different from the above-described systemic therapies in that they target specific inflammatory pathways and are administered subcutaneously (s.c.) (or intravenously i.e., infliximab) on different weekly schedules. Biologics presently target two pathways crucial in the development and chronicity of the psoriatic plaque: the IL-23/Th17 axis and TNF- α -signaling (see [Table 3](#)).

TNF- α

TNF- α inhibitors have been available for over a decade. They are considered the first-generation biologics, and are effective for plaque psoriasis and psoriatic arthritis. TNF- α inhibitors are still the standard used to evaluate drug efficacy in psoriasis

clinical research. There are currently four drugs in this category: etanercept, infliximab, adalimumab, and certolizumab. Etanercept is unique in the biologics category in that it is not a monoclonal antibody, but rather a recombinant human fusion protein. The receptor portion for the TNF- α ligand is fused to the Fc portion of an IgG1 antibody. It was the first TNF- α inhibitor approved by the United States Food and Drug Administration (FDA) for psoriasis. Infliximab is a chimeric monoclonal IgG1 antibody, and adalimumab is a fully human monoclonal IgG1 antibody. They neutralize TNF- α activity by binding to its soluble and membranebound form. These drugs are particularly employed to treat psoriatic arthritis, and show a similar efficacy. In the treatment of psoriasis, they show different PASI 75 response rates: 52% for etanercept, 59% for adalimumab, and 80% for infliximab. Infliximab shows superiority in terms of efficacy when compared to the other TNF- α inhibitors, and when compared with ustekinumab, it showed a similar performance. The chimeric nature of infliximab might contribute to a higher immunogenic potential of the drug, which in turn might influence drug survival. Certolizumab pegol is a pegylated Fab' fragment of a humanized monoclonal antibody against TNF- α . PEGylation is the covalent conjugation of proteins with polyethylene glycol (PEG), and is attributed a number of biopharmaceutical improvements, including increased half-life and reduced immunogenicity. The initial indication for treating Crohn's disease was extended to psoriatic arthritis and recently to plaque psoriasis. Certolizumab has shown an 83% PASI 75 response. Unlike other anti-TNF- α agents, it has no Fc domain, and is thus not actively transported across the placenta. Thus, certolizumab pegol is approved for use during pregnancy and breastfeeding.

IL23/TH17 Axis

As previously mentioned, IL-23 drives the expansion of Th17 cells whose inflammatory effects are in turn mediated by IL-17A, IL-17F, and IL-22. IL-23 is a dimer composed of p40 and p19. The first biologic to be approved for psoriasis vulgaris after the TNF- α inhibitors was ustekinumab, which is a monoclonal antibody directed against the p40 subunit. P40 is not exclusive to IL-23, but rather is shared with IL-12. IL-12 is a dimer consisting of p40 and p35, and is involved in the differentiation of naïve T cells into Th1 cells. By targeting p40, ustekinumab blocks two different T-cell activating mechanisms, namely Th1 and Th17 selection. Ustekinumab is also effective for the treatment of PsA and Chron's disease. It is available in two dosages, 45 mg and 90 mg, depending on a threshold body weight of 100 kg.

Ustekinumab has extensive safety data, few side effects, good clinical efficacy, and long treatment drug survival was reported. At 90 mg, ustekinumab showed a PASI 75 response in 72.4% and in 61.2% at 45 mg. Studies using real-life data compared ustekinumab with the anti-TNF α drugs, and ustekinumab was found to have a significant longer drug survival. Tuberculosis (TB) has only been reported in two psoriasis patients receiving ustekinumab. On the other hand, Th1 signaling is important for the response against bacterial and viral pathogens, and a study showed IL12 signaling to have a protective effect in a model of imiquimod psoriasis-like inflammation. This rationale fueled the development of drugs targeting p19, which is the IL-23-exclusive subunit. This more specific molecular targeting approach has also achieved successful clinical outcomes. Three fully human monoclonal antibodies with p19 specificity are available: guselkumab, tildrakizumab, and risankizumab. Guselkumab is licensed for psoriasis, and showed clinical superiority when compared to adalimumab, with 85.1% of patients reaching a PASI 75, and 73.3% receiving a PASI 90 response at week 16. Patients receiving tildrakizumab showed a 74% PASI 75, and 52% PASI 90 at week 16.

Tildrakizumab was compared to etanercept, and was more likely to reach PASI 75 at weeks 16 and 28. Risankizumab showed the following PASI responses at week 12: 88% PASI 75, 81% PASI 90, and 48% PASI 100. Patients were followed for 48 weeks after the last injection at week 16, and one-fourth of them showed a maintained PASI 100. Whether IL-23 inhibition has the potential to modify the course of the disease after subsequent drug retrieval is currently under study.

Biosimilars In Psoriasis

The introduction of biosimilars for different diseases is revolutionizing the pharmaceutical arsenal at hand. As patents for many biologics face expiration, biosimilar versions of these drugs are being developed, or are already entering the market. A biosimilar is a biological product that must fulfill two requirements: it must be highly similar to an approved biologic product and have no clinically meaningful differences in safety, purity, or potency when compared with the reference product. Guidelines for the development and approval of biosimilars have been issued by the European Medicines Agency, the FDA, and the World Health Organization. There are currently eight adalimumab biosimilars, four infliximab biosimilars, and two etanercept biosimilars approved in Europe. By lowering the costs of

systemic treatment for psoriasis patients, biosimilars may also increase access to biologics.

Drugs In The Research Pipeline

Tofacitinib is an oral Janus kinase (JAK) inhibitor currently approved for the treatment of rheumatoid arthritis (RA) and PsA. Tofacitinib showed a 59% PASI 75 and 39% PASI 90 response rate at week 16, and was also effective for nail psoriasis; however, its development for psoriasis was halted for reasons unrelated to safety. Upadacitinib is another JAK inhibitor currently undergoing phase III clinical trials for the treatment of psoriatic arthritis. Two different biologics targeting IL-17 and one targeting IL-23 are being currently tested. In addition, there are currently 13 registered phase III clinical trials testing biosimilars for adalimumab (eight), infliximab (three), and etanercept (two).

HERBAL DRUGS

- i. Yarrow
 - ii. Plantain
 - iii. Peppermint
 - iv. St John's Wort v. Arnica
 - v. Goldenseal
- Yarrow

Internally: fights infection, stimulates sweating + lowers fever. Strengthens circulation, blood flow.

Relieves digestive distress & cramping.

Externally: antibacterial + anti-fungal. Used topically to staunch bleeding as well as to treat cuts, scrapes, burns, and rashes

Plantain

Internally: anti-inflammatory, often used to ease coughs + mucous membrane irritation.

Externally: as a poultice chew or mash leaf to apply on bites, stings, burns, cuts

Peppermint

Internally: anti-inflammatory, often used to ease coughs + mucous membrane irritation.

Externally: as a poultice - chew or mash leaf to apply on bites, stings, burns, cuts + scrapes

ST JOHN'S Wort

Internally: Powerful antiviral and antimicrobial used to fight off viruses and infections. Also a nervine soothes the nervous system.

Externally: for arthritic joints, burns, sunburns and stings. Due to its antibacterial properties it is also good for wounds and skin irritation

Arnica

Internally: use in homeopathic form to relieve muscle pain & stiffness, pain, swelling + discoloration from bruises.

Externally: cream or salve can be used for muscle pain, bruising + sprains

Goldenseal

Internally: contains berberine which has antibiotic action. Helps fight off infections and has been known to help digestive distress such as travelers diarrhea.

Externally: can be applied onto cuts or wounds to stop



Plantain



Peppermint

**Arnica****St John's Wort****Yarrow****Goldenseal****CONCLUSION:**

Psoriasis is a complex multifactorial disease for which various novel therapies have arisen in the past years. In spite of the refinement of the targeted therapies, psoriasis remains a treatable but so far not curable disease. The targeted therapies show high clinical efficacy for the inhibition of IL-23 and IL17. Some degree of a persistent antipsoriatic effect by these therapies could be demonstrated after drug discontinuation, and argue for disease modification concept. This important finding will be followed up in ongoing and future studies. However, in other cases,

an initial clinical response is only short lived, requiring treatment with a different biologic. Clearly, more research is required to answer the question of why the drug survival of some biologics is limited. The therapeutic arsenal for psoriasis is likely to increase in the near future, with studies on orally applied new small molecules such as inhibitors targeting ROR γ t. In spite of the safety and efficacy of targeted therapies, due to economic factors, dosage regimes, and adverse effect profiles, broader-acting drugs remain the mainstay of psoriasis systemic therapy in many clinical scenarios around the world.

The role of genetics remains to be elucidated not only in the context of predisposition to disease, but also in the profiling of distinct psoriatic types based on cytokine signatures, and in identifying therapy response markers. Clearly, psoriasis is currently the best understood and the best treatable Th17-biased chronic inflammatory disease. After achieving excellent clinical responses for the majority of patients with available therapeutic approaches, the stratification of psoriasis patients to the optimal drug and ensuring the sustainability of our treatments are the major tasks to be resolved.

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