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Revolutionary Target-Based Approaches Inscribing the Pathogenesis of Psoriasis

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ABSTRACT

Psoriasis is a chronic, non-communicable, painful, disfiguring, and disabling disease for which there is no cure and it considerably affects a patient's quality of life. This article has considered an in-depth review using various search methodologies which describes the pathogenesis of psoriasis and target-based approaches. The findings in pathogenesis include many approaches from epidermal hyperplasia to immune-mediated, chronic inflammatory, genetic and autoimmune mechanisms. Psoriasis seems to be a feedback system of immune cells running beneath the skin. The development of precisely targeted therapy is possible with a detailed understanding of disease pathophysiology. So, the present review comprises insights into pathophysiology and target-based approaches for psoriasis therapy.

Keywords: Pathogenesis, Targets, Immune cells, cellular mechanisms, Signal transduction pathways, biologics

INTRODUCTION

Psoriasis is a chronic disease for which there is no clarity on etiology, although genetic predisposition is evident. Although, there is a suggestion that psoriasis could be categorized as an autoimmune disease. Psoriasis can also be provoked by external and internal triggers, including mild trauma, sunburn, infections, systemic drugs, and stress-producing localized or generalized skin lesions, which are red patches usually covered with a white or silvery scale. The clinical feature of psoriasis differs by different types of psoriasis. Based on the pathogenesis of psoriasis, various targets are being identified leading to precise treatment of psoriasis disease. Epidemiologically, the burden of psoriasis is high and the prevalence of the disease varies in different regions. By describing the approaches in pathogenesis and highlighting the targets associated with the disease, the general management of psoriasis is possible using topical therapies, phototherapy, non-biologics, and biologic agents.

Search methodologies for preparation of review

For preparing this review, we have used PubMed and non-PubMed databases. In these databases various search terms: Psoriasis Targets, Management of Psoriasis, Treatments for Psoriasis, Biologics and Non-biologics; are used to obtain the appropriate literature. The eligibility of articles is determined by reading the title and abstract of each identified article. In addition to this, the drug target database was also searched for target identification and for reviewing the functions of targets. Clinical guidelines of psoriasis were also searched for identifying general management of psoriasis.

Clinical presentation of psoriasis

In psoriasis, the skin lesions are localized or generalized, most symmetrical, well-demarcated, with red papules and patches,

and usually covered with white or silvery scales. The lesions are itching, burning and painful. The most commonly reported symptoms are scaling of the skin, itching, erythema, fatigue, swelling, burning, and bleeding. [1] Although the clinical features of psoriasis may differ among the variants of psoriasis (Figure 1).[2]

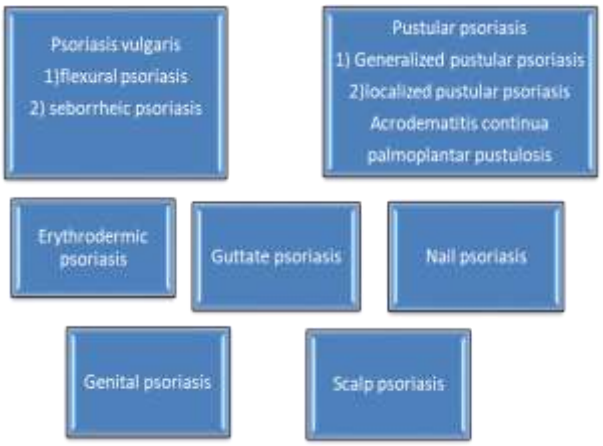

Figure 1. Types of Psoriasis

Epidemiology

There was an attempt to measure the degree of disability or loss of health due to different diseases by the 2010 Global Burden of Disease Study. One of the commonly used matrices for this measure is the Disability Adjusted Life Year (DALY). DALY is equal to the sum of years lived with a disability (YLD) and years of life lost (YYL). 1 DALY is equal to one year of healthy life lost. Analysis of the global burden of disease study suggests that the burden of psoriasis is high. The prevalence of the disease varies according to the burden of suffering and the population affected from country to country.[1]

Pathogenesis of psoriasis

Many theories were proposed regarding pathogenesis, which has led to a proper understanding of the disease's pathophysiology (Figure 2). [3–6]

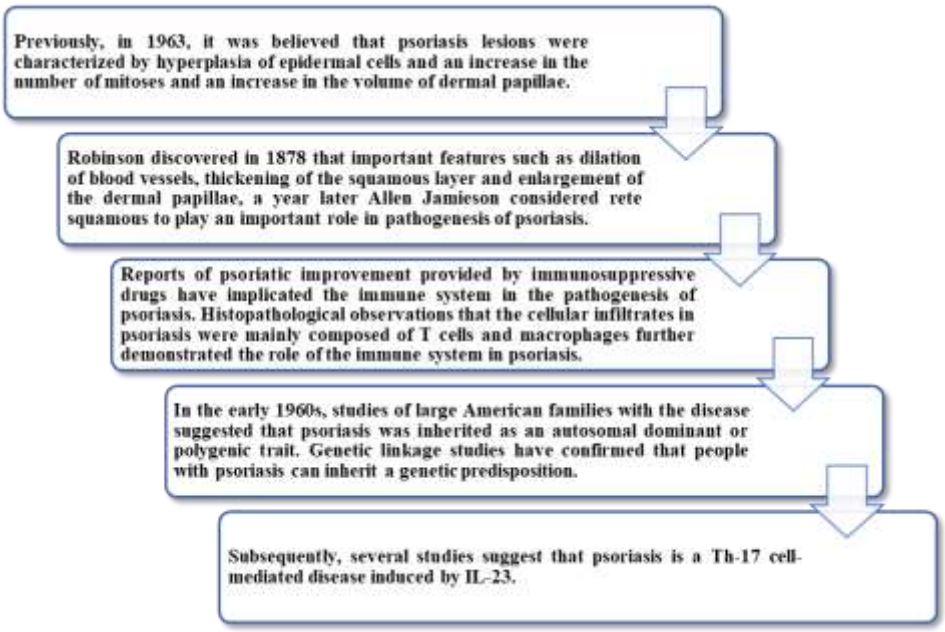

Figure 2. Approaches to the understanding of pathophysiology

In addition to the major role of the immune system, the genetic and environmental factors associated with psoriasis include cellular and molecular mechanisms and the role of major cell signaling pathways.

Genetic factors in the development of psoriasis

Psoriasis is a multifactorial genetic disease whose genetic factors explain about 70% of the susceptibility to the disease. An increased incidence of psoriasis has been reported in families around the world.[7]

The first studies that attempted to shed light on the genetics of psoriasis were based on linkage analysis, a statistical approach that allows the localization of disease genes in well-defined chromosomal regions. In the case of psoriasis, linkage analysis identified nine different regions (termed psoriasis susceptibility (PSORS) 1-9) that were considered to contribute to disease susceptibility.[8] Recently, Human-Like antigen (HLA-Cw6) has been identified as the susceptibility allele of PSORS1 and it is proven as the main contributor to the molecular pathogenesis of psoriasis. Considering the role of HLA-C in antigen presentation, it was hypothesized that HLA-Cw6 might have a high binding affinity for one or more psoriasis autoantigens. LL-37, which is an antimicrobial peptide and disintegrin-like and metalloprotease domain which contains thrombospondin type 1 motif-like 5 (ADA MTSL5) has been reported to bind HLA-Cw6. LL-37 has been reported as an autoantigen of T-cell in psoriasis. [7,8]

Recent studies using immune chip platforms, the entire genome, and exome-wide studies have identified up to 63 sites of susceptibility to psoriasis and throughout these decades, at least 100 susceptibility genes for psoriasis are identified, among which most are involved in adaptive immunity, innate immunity, and skin barrier function. [9] The various genes involved in psoriasis and their functions are listed in Table 1. [9,10]

Table 1: List of genes involved and their function

Candidate genes	Function in which they are involved
HLA-c, ERAP1 and ERAP2	Antigen presentation
IFIH 1, DDX58, RNF114 and TYK2	Innate immune regulation
CARD14, TNFAIP3, TNIP1 and NFkB1A	NF-kB regulation
IL12Bp40, IL23Ap19, IL23R and TRAF3IP2	Activation of IL-23 / IL-17
IL36RN and AP1S3	Activation of IL-36
VEGFA	As a main proangiogenic factor

Environmental factors

Environmental factors such as diet and obesity, smoking and alcohol consumption, physical trauma, drug reactivity, and microbial infections trigger psoriasis. Several studies have provided evidence of the dominant pathway IL-23 / IL-17 in the pathogenesis which is regulated by metabolites produced by the gut and skin microbiota.[10,11]

Cellular and molecular mechanisms of pathogenesis

Psoriasis is a complex disease wherein there is an interaction between immune cells, keratinocytes, and other resident skin cells such as endothelial and immune cells. The contribution of each cell type is crucial in the initiation and maintenance phases of psoriatic disorders. [12]

Another trigger for psoriasis is the deregulated immune response in skin lesions which also plays an important role in maintaining the development of the psoriasis response. The pathogenesis of psoriasis is understood at two level mechanism, cellular and molecular levels:

- Cellular level: Uncontrolled proliferation and differentiation of keratinocytes and infiltration of immune cells are associated at the cellular level
- Molecular level: Robust production by these cells which produces

proinflammatory cytokines in the psoriatic sites.[10]

The interplay between these molecular and cellular participants of psoriasis forms a feedback loop, further inducing the extent and duration of psoriatic inflammation.

There are 3 major populations of Dendritic Cells (DC) in the skin, they are Langerhans cells (LCs), plasmacytoid cells (pDCs), and myeloid DCs (mDCs). The activation of LCs in the epidermis promotes their translocation to draining lymph nodes where T-cell activation is initiated. They activate Th17 and Th22 differentiations. Plasmacytoid cells produce Tumor Necrosis Factor (TNF-α), IL-1β, and IL-6 and a significant amount of interferon IFN-α. Myeloid or Langerhans cells are the main cells activated during the pathogenesis of psoriasis.

$CD11C^{+}$ - blood dendritic cell antigen (BDCA) -1^{+} is the main resident cutaneous DC population found in normal skin. It has now been discovered that psoriatic lesion skin has two populations of dermal DCs:

1) $CD11C^{+}$ $BDCA\text{-}1^{+}$ cells, phenotypically similar to those available in normal skin.
2) $CD11C^{+}$ $BDCA\text{-}1^{-}$ cells, phenotypically immature and producing inflammatory cytokines. This increases by 30 folds in psoriasis.

Inflammatory mDCs, produce TNF-α, IL-6, IL-12, IL-20, and IL-23, which are cytokines with critical roles in driving T-cell differentiation into Th1 and Th17 phenotypes. [10,13]

Cluster of Differentiation 4 ($CD4^{+}$) based cytokines, helper T cells (Th) can be divided into subsets, viz. regulatory T (Treg), Th1, Th2, and Th17. Treg cells are immunosuppressive and generally suppress effector T cell proliferation via secreting immunosuppressive cytokines, including transforming growth factor beta (TGF β), IL-10, and IL-35; their decreased levels are reported in psoriasis as the activity of Treg cells is impaired in psoriasis. Antigen-activated T cells produce IL-2 which acts on IL-2 receptors in Treg cells, alerting them to strong T cell activity in the environment so that Treg cells generate a suppressive response. Tregs are distinguished by the expression of CD4, CD25, and Forkhead box P3 (FOXP3). Th1 cells are associated with the release of IFN-γ, TNF-α, and IL-12. Th2 cells express the transcription factor GATA binding protein 3 (GATA-3) and lead to the production of IL-4, IL-5, and IL-13. IL-1β, IL-6, and IL-23 drive the differentiation of Th17 cells. Th17 cells produce signature retinoic-acid-receptor-related orphan nuclear receptor gamma T (RORγT) and release IL-17, TNF-α, IL-21, IL-22, and IL-26. These cells are the main source of IL-17, which plays a crucial role in the development of psoriasis. [10] The DCs which are infiltrating at psoriatic sites produce IL-23 to maintain the IL-17 generating T cells.

Keratinocyte activation plays a key role in a feedback loop in the IL-23/IL-17 driven inflammation. IL-17A's synergy with other cytokines, such as TNF-α and IL-22, stimulates the production of antimicrobial peptides (AMPs), inflammatory cytokines, chemokines, and chemo-attractants in keratinocytes. AMPs include LL-37, the S100 A family of proteins, β-defensins, and lipocalin-2. They are associated with innate immunity regulation which protects the skin from infections. Cytokines such as TNF-α, IL-1, IL-6, IL-8, IL-17, IL-19, IL-20, and IL-36 are responsible for driving the inflammatory loop in psoriasis. C-C motif ligand (CCL)20, a chemokine plays an important role in recruiting C-C motif chemokine receptor (CCR) 6^{+} cells, such as T cells producing IL-17 and some DCs. The chemokine (C-X-C motif) ligand 1 (CXCL1), CXCL 3, and CXCL 8 are the chemo-attractants that attract neutrophils and sustain their activation and survival, contributing to the production of AMPs and pro-inflammatory cytokines.

In psoriasis, B cells have been detected in damaged skin and altered frequencies of circulating B cells have been described in psoriasis. Still, the functional role of B cells in the disease-specific immunology of

psoriasis is unclear.[10]

Main cell signal transduction pathways involved in psoriasis

Cellular and molecular immunomodulators in the development of psoriasis are embedded in several important signal transduction pathways, as a result, they activate transcription factors including nuclear factor kappa B (NFkB), interferon regulatory factors (IRFs), and signal transducer and activators of transcriptions (STATs) in cells.

Toll-like receptors (TLR) agonists, IL-1, IL-17, IL-36, and TNF-α activate the NFkB signaling pathway to promote the transcription of several genes encoding inflammatory mediators and cytokines, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), IL-1β, IL-6, IL-12, IL-23, and TNF alpha. Many cytokines as listed above acts on cells via binding with G-Protein coupled receptors and then stimulating the JAK-STAT pathway. [10] In the JAK/STAT pathway out of the various STATs, STAT-3 is hyperactivated in immune cells and keratinocytes. Activation of STAT-3 in keratinocytes inhibits cell differentiation, promotes proliferation, and produces antimicrobial peptides. [9] The pathogenesis of psoriasis is well described in (**Error! Reference source not found.**).

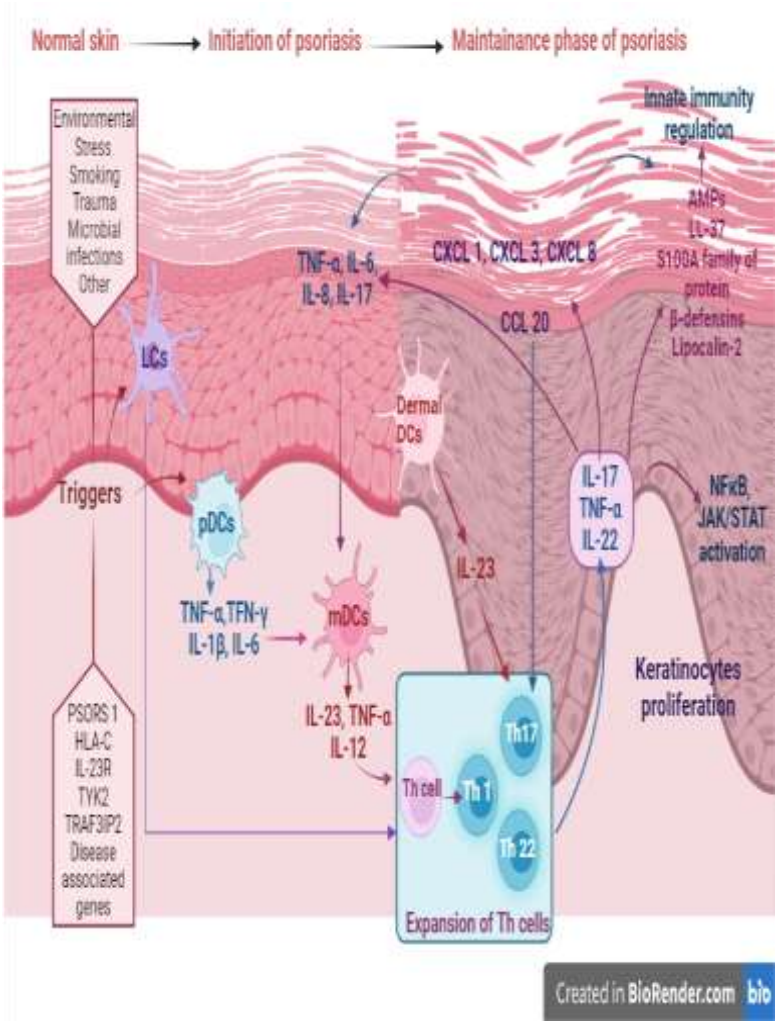

Figure 3. Pathogenesis of psoriasis

An overview of the general management of psoriasis

The management of psoriasis includes topical treatments, phototherapy, non-biologics, and biologics therapies (Figure 4). [14,15]

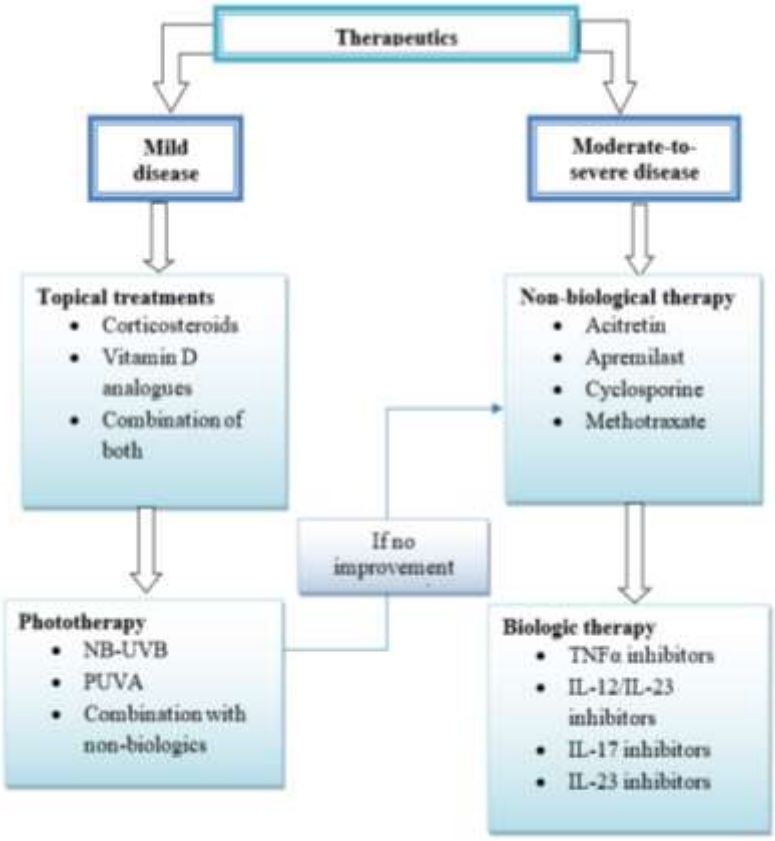

Figure 4. Management of psoriasis

The treatment choices for psoriasis are based on the severity of disease, mild disease can be managed by topical therapy and moderate-to-severe disease requires systemic therapy for controlling disease and can also be given with concomitant topical therapy. Though the side effect profiles of all these therapies are high, special emphasis should be given on target-based treatments. By targeting various inflammatory mediators involved in the psoriasis pathogenesis, development of drugs with favourable safety profile and limited side effects along with efficacious results is possible.[16]

Therapeutic targets for psoriasis

Based on an understanding of the pathogenesis of psoriasis, we have focused on possible targets for the treatment of psoriasis. In this review, using the therapeutic target database, we have enlisted various targets for psoriasis along with their functions. In addition to that, the drugs approved for that target and the drugs which are in phase 3 clinical trial are also listed in table 2 [17-19].

Table 2: Description of various targets for psoriasis along with their functions and associated drugs

Target for psoriasis	Function	Approved drugs	Drugs in phase 3 trials
Vitamin D3 receptor (VDR)	Activate the transcription of vitamin D3-responsive target genes. It plays a crucial role in calcium homeostasis.	Calcipotriol	
Aryl hydrocarbon receptor	AhR is a ligand dependent transcription factor which is highly expressed in keratinocytes.	Tapinarof	
Retinoic acid receptor gamma (RARG)	Retinoic acid receptors bind as heterodimers to their target response elements in response to their ligands, all-trans or 9-cis retinoic acid, and regulate gene expression in various biological processes.	Tazarotene	
Signal transducer and activator of transcription 3 (STAT3)	Acts as a regulator of the inflammatory response by regulating differentiation of naive CD4(+) T-cells into T-helper Th17 or regulatory T-cells (Treg). Involved in cell cycle regulation by inducing the expression of key genes for the progression from the G1 to S phase.	Acitretin	
TYK2 tyrosine kinase (TYK2)	Probably involved in intracellular signal transduction by being involved in the initiation of type I Interferon (IFN) signalling. Interferon-α/β receptor α chain phosphorylation.	Deucravacitinib	
Calcineurin	Calcium-dependent, calmodulin-stimulated protein phosphatase plays an essential role in the transduction of intracellular Ca^{2+} mediated signals.	Ciclosporin	
PDE-4 inhibitors	The enzyme hydrolyses cAMP and mediates inflammatory responses, its inhibitors activate some downstream pathways by increasing cAMP and suppresses inflammatory response.	Apremilast Roflumilast	Mufemilast
Cyclin-dependent kinase 6 (CDK6), & CDK4	It is involved in the initiation and maintenance of cell cycle exit during cell differentiation; prevents cell proliferation and regulates negatively cell differentiation, but is required for the proliferation of specific cell types (e. g. erythroid and hematopoietic cells).	Apremilast	
Cytoplasmic thioredoxin reductase (TXNRD1)	Isoform 1 may possess glutaredoxin activity as well as thioredoxin reductase activity and induces actin and tubulin polymerization, leading to the formation of cell membrane protrusions. Isoform 4 enhances the transcriptional activity of estrogen receptors alpha and beta while isoform 5 enhances only the beta receptor and also mediates cell death induced by a combination of interferon-beta and retinoic acid.		Spermidine
A3 Adenosine receptor	Gi associated protein coupled receptor found overexpressed in psoriasis patients on the peripheral blood mononuclear cells. And upon activation it downregulates the NFκB pathway.		Piclodenoson
Janus kinase 3 (JAK-3) & (JAK-1)	Mediates essential signalling events in both innate and adaptive immunity and plays a crucial role in hematopoiesis during T-cells development.		Peficitinib Tofacitinib
Tumor necrosis factor (TNF)	It is mainly secreted by macrophages and can induce cell death of certain tumor cell lines. Impairs regulatory T-cells (Treg) function via FOXP3 dephosphorylation. Upregulates the expression of protein phosphatase 1 (PP1), thereby inactivating FOXP3 and providing Treg cells functionally defective.	Adalimumab Certolizumab Etanercept Infliximab	
Interleukin-17 (IL17)	It is involved in inducing stromal cells to produce proinflammatory and hematopoietic cytokines.	Brodalumab Ixekizumab Secukinumab	Bimekizumab Netakimab Vunakizumab
Interleukin-23 (IL23), Interleukin-37 (IL37)	It binds to a heterodimeric receptor complex composed of IL12RB1 and IL23R and activates the Jak-Stat signalling cascade, stimulates memory rather than naive T-cells, and promotes the production of proinflammatory cytokines.	Guselkumab Risankizumab Tildrakizumab Ustekinumab	Mirkizumab
Interleukin-12α(IL12A), Interleukin-12β(IL12B)	A cytokine that can act as a growth factor for activated T and NK cells, enhance the lytic activity of NK/lymphokine-activated killer cells.	Ustekinumab	
IL-36	It activates the downstream pathways NFκB and MAPK and promotes chemokine release.	Spesolimab	Imsidolimab

Target based treatment approaches

Calcipotriol

It is a topical vitamin D analog which bind to vitamin D receptors on T cells and vitamin D receptors on keratinocytes to stop keratinocyte proliferation and stimulate keratinocyte differentiation.[2]

Vitamin D analogs are more effective than topical vitamin A derivatives (retinoids), coal tar, and placebo for psoriasis of the trunk and extremities.[20] It is reported to cause rarely skin irritation, hyperglycemia, hypercalciuria, and parathyroid hormone suppression. [21]

Tapinarof

Tapinarof cream 1% is an aryl hydrocarbon receptor (AhR) modulator, which was approved by Food and Drug Administration (FDA) for plaque psoriasis on 24 may 2022.

PSORING-1 and PSORING-2 which are two identical phase 3 trials, 0 or 1 Physician Global Assessment (PGA) score was obtained in significantly greater proportion of participants by once daily tapinarof cream.

With some advents of folliculitis, contact dermatitis and headache the drug was well tolerated among the patients. [19]

Tazarotene

Vitamin A derived topical retinoid, works by normalizing the function of keratinocytes and anti-inflammatory action, modifying the transcription of the genes in keratinocytes.[20,21] For the treatment of mild to moderate psoriasis, topical application of tazarotene for 8 to 12 weeks have shown effective results in several studies. [24] It may cause erythema, burning, itching, and localized irritation[21,23]

Acitretin

The oral retinoid, approved for the treatment of psoriasis by the FDA in 1997. [22] It promotes the activation of nuclear retinoic acid receptors Retinoid acid receptor-α (RAR-α), -β, -γ and regulates gene transcription. [25] This medication is contraindicated in pregnancy, hypercholesterolemia, myalgia, alopecia, xerosis, rhinitis, retinoid dermatitis, and xerophthalmia.

Acitretin is widely used as combination therapies, as it is alone less beneficial than other common systemic therapies. [22,25]

Deucravacitinib

It is an oral Tyrosine kinase 2 (TYK2) inhibitor, approved for the treatment of moderate-to-severe plaque psoriasis on 9 September 2022 by FDA. In POETYK Pso-1, a 52 weeks phase 3 trial, a Psoriasis Area Severity Index (PASI 75) response was achieved in significantly greater proportion of participants.

The most common adverse events associated are upper respiratory tract infections and nasopharyngitis. [19]

Ciclosporin

It is a potent immunosuppressant that works by binding to cyclophilin, which then inhibits calcineurin and blocks pro-inflammatory signalling.

When cyclosporine was dosed at 2.5 to 5 mg/kg/d for 12 to 16 weeks, a dramatic improvement was observed in up to 80% to 90% of patients with psoriasis, but these patients frequently relapse after discontinuation if other treatments are not substituted. Nephrotoxicity and hypertension are the most common side effects of cyclosporine. Renal function is impaired in many patients. [20–22]

Apremilast

Apremilast is a first oral phosphodiesterase-4 (PDE-4) inhibitor that was approved by the US FDA in 2014. It Inhibits phosphodiesterase-4, resulting in an elevated level of intracellular cyclic adenosine monophosphate (cAMP), with subsequent downregulation of inflammatory responses involving Th 1, Th 17, and the interferon pathway.

One randomized clinical trial (RCT) reported that use of apremilast resulted in to PASI 75 at week 32 in psoriasis patients. When used in conjunction with other therapies like biologics, beneficial effects were observed in multiple case reports and small case series. It may lead to nausea, diarrhea, headache, upper respiratory tract infection, and nasopharyngitis.[22]

Roflumilast

It is a topical PDE 4 inhibitor that was approved on 20 July 2022 for the treatment of plaque psoriasis in patients greater than 12 years of age.

Once daily application of cream for 8 weeks, resulted in 42.4% and 37% of patients randomized to roflumilast treatment and 6% and 6.9% of patients randomized to the vehicle treatment in DERMIS-1 and DERMIS-2 trials, respectively, achieved Investigator's Global Assessment (IGA) score success at 8 weeks.

Low rates of application site reactions were observed with roflumilast treatment, and the commonly reported treatment emergent adverse events includes hypertension, headache, diarrhea and nasopharyngitis.[19]

TNFα Inhibitors

Adalimumab

It is a human monoclonal Immunoglobulin G1 (IgG1) antibody that binds to soluble membrane-bound TNF-α, blocking its interaction with TNF receptors.[2,26] It was approved for the treatment of adults with moderate to severe plaque psoriasis.

In efficacy assessment of adalimumab in phase 3 RCT for the treatment of moderate-to-severe plaque psoriasis, at week 16 PASI 75 was observed in 71% and PASI 90 was observed in 45% of patients treated with adalimumab. [26]

Certolizumab

It is a humanized antigen-binding fragment of a monoclonal antibody and binds to TNF-α, antagonizing its interaction with TNF receptors. Unlike other biologics, certolizumab pegol is not transferred into breast milk and has little or no placental transfer. [26] It is an efficacious treatment for plaque psoriasis and for that approved dose is of 400 mg for moderate-to-severe psoriasis. [26]

Etanercept

It is a fusion protein between a TNF-α receptor protein and the crystallizable fragmented part of IgG1. It works by competitively inhibiting the binding of TNF-α to TNF 1 and 2 receptors.[2] It is approved for the treatment of moderate to severe plaque psoriasis in children and adults, psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis.[26] In a pooled analysis, etanercept administered 50 mg twice weekly or 50 mg once weekly, significant proportion of patients achieved 75% improvement in the PASI as compared to placebo. [26]

Infliximab

Infliximab is a chimeric monoclonal antibody that consists of a mouse variable region and a human IgG1 alpha constant region. Infliximab binds to soluble and transmembrane TNF-α molecules, neutralizing the effects of TNF-α. Infliximab is approved for the treatment of psoriasis in adults and also approved by FDA for the treatment of Crohn's disease and ulcerative colitis in both adults and children. [26] In RCT, infliximab administered with 5 mg/kg dose at standard dose interval, PASI 75 was observed at week 14.[26]

With most TNF-α inhibitors a complete response to treatment is best observed at 12 to 16 weeks of continuous therapy, while in case of infliximab it is observed after 8 to 10 weeks. [26] Adverse effects associated with TNF- α include serious infections, malignancy, neurological diseases, congestive heart failure, pancytopenia, Hypersensitivity reactions, lupus-like syndrome, autoimmune hepatitis, injection site reactions and infections, and latent reactivation of hepatitis B infections. [20]

IL-17 Inhibitors

Brodalumab

It is a human IgG2 monoclonal antibody that targets the IL-17 pathway by binding to the IL-17A receptor. It is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and who have not responded or lost response to other systemic therapies. Two phase 3 studies (AMAGINE-2 and AMAGINE-3) reported that at week 12, 86% and 67% patients achieved PASI 75 respectively.[26]

Ixekizumab

It is a human IgG4 monoclonal antibody that binds to the cytokine IL-17 A. It was approved for the treatment of adults having moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. In a phase 3 RCT

(UNCOVER-3) at week 12, patients receiving 80 mg drug every 4 weeks 84.2% patients achieved PASI 75 and 65.3% achieved PASI 90 and 35% achieved PASI 100.[26]

Secukinumab

It is a humanized IgG1 monoclonal antibody that targets IL-17A and is the first Il-17 antibody on the market for the treatment of psoriasis in adults and use in psoriatic arthritis and severe psoriasis of the scalp. Secukinumab is also effective in generalized pustular, erythrodermic, and palmoplantar psoriasis of the head, neck, and nails.[26]Multiple RCTs confirmed the efficacy of secukinumab, in 2 phase 3 RCTs, ERASURE and FIXTURE, the significant proportion of patients achieved PASI 75 at week 12.

Complete response to treatment with IL-17 inhibitors is best observed with continuous therapy after 12 weeks. In patients responding partially to treatment dose escalation should be considered. [26] Its adverse effects include nasopharyngitis, upper respiratory tract infection, other infections, nausea, diarrhea, hives, and rhinorrhea.[20]

IL-23 Inhibitors

Guselkumab

It is a fully human IgG1 lambda monoclonal antibody that blocks the p19 subunit of IL-23. It is an FDA-approved product for moderate to severe plaque psoriasis in adults.

In a phase 3 RCT, VOYAGE 2, guselkumab is compared with adalimumab or placebo, at week 16, a significant proportion of patients achieved PASI 90 receiving guselkumab for the treatment of moderate-to-severe psoriasis. [26]

Risankizumab

It is a humanized IgG1 monoclonal antibody that binds to the p19 subunit of Il-23, thereby inhibiting this key cytokine and its role in psoriatic inflammation. In RCT, patients receiving risankizumab,77% of them achieved PASI 90 as compared to 40% patients in ustekinumab group at week 12. [26]

Tildrakizumab

This is a novel high-affinity humanized IgG1 lambda monoclonal antibody designed to selectively block IL-23 by binding to the p19 subunit. It was approved by the FDA for the treatment of moderate to severe plaque psoriasis.[21,26]

In phase 3 clinical trial, tildrakizumab at the dose of 100 mg or 200 mg at week 0 and 4 following every 12 week administration, showed effective results for the treatment of adult moderate-to-severe psoriasis. [26]

By various clinical trials and analysing real life data, guselkumab, risankizumab and tildrakinumabare confirmed as effective and safe treatment in clinical practice, it has also showed excellent results in more fragile patients such as elder populations and also in patients with multiple comorbidities, with no serious adverse events reported.[26]

IL-12/IL-23 Dual Inhibitor

Ustekinumab

It is a dual inhibitor that targets IL-23 and IL-12. It is a human monoclonal antibody that binds with high specificity and affinity to the p40 subunit of IL-12 and IL-23, thereby suppressing IL-mediated inflammation, in which IL-12 and IL-23 are associated with psoriasis.[20]

In RCT PHOENIX 1 at the dose of 45 mg, the PASI 75 response at week 12 is observed in 67.1% and at the dose of 90 mg it was observed in 66.4% patients while in case of placebo it was 3.1%.[26]

Its use may lead to infection, reactivation of latent infection, skin cancer other than melanoma, hypersensitivity reactions, posterior leukoencephalopathy syndrome, non-infectious pneumonia, nasopharyngitis, upper respiratory tract infection, headache, and fatigue.[20]

IL-36 Inhibitor

Spesolimab

It is a humanized, anti-IL-36 receptor monoclonal antibody, which was approved for the treatment of Generalized Pustular

Psoriasis (GPP) flares by the FDA on 1 September 2022.

In the phase 3 trial Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 was obtained in 54% patients while 0 or 1 score was obtained for 43%.

The most common adverse effects associated are infections.[19]

CONCLUSION

Psoriasis seems to be a complex disease involving both chronic inflammatory and autoimmune as well as some genetic determinants in its mechanism. This disease greatly affects a patient's well-being and is associated with many psychosocial conditions. It has been suggested from our review that it can be well controlled and eradicated with the advent of target-based therapy using biologics, nonbiologic and topical therapy.

Declaration by Authors

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