



Review Article

Multi modal targets in Psoriasis

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ABSTRACT

Psoriasis is a life-long disease that requires long-term treatment. The long-term use of conventional systemic treatments is limited mostly by poor tolerability and cumulative toxicity. Psoriasis significantly impairs the quality of life of patients. In contrast, the long-term use of biologics is more advisable, because of better tolerability and safety, although their cost hinders their clinical usage. Evidence suggests that PASI 100 (i.e., complete clearance of psoriasis) may be achievable for many patients with moderate-to-severe psoriasis using biologics in development brodalumab and ixekizumab or secukinumab that inhibit interleukin (IL)-17.

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1. Introduction

Psoriasis is a chronic, noncommunicable, painful, disfiguring and disabling hyperproliferative disease with increased rate of epidermal turnover, for which there is no cure, presenting without a single, typical clinical picture.¹ The commonest form of psoriasis is plaque psoriasis in which patients may have sharply circumscribed, round-oval, or coin-sized plaques. The lesions may initially begin as erythematous macules (flat and <1 cm) or papules, extend peripherally, and coalesce to form plaques of one to several centimetres in diameter. Guttate psoriasis, describes the acute onset of a myriad of small, 2–10 mm diameter lesions of psoriasis. Inverse Psoriasis affecting the flexures, particularly inframammary, perineal, and axillary, is distinct morphologically from traditional plaques elsewhere on the trunk and limbs. Generalised pustular psoriasis is rare and represents active, unstable disease. *Psoriatic nail disease*: Fingernails are more commonly affected than toenails. The commonest finding is small pits in the nail plate, resulting from defective nail formation in the proximal portion of the nail matrix.²

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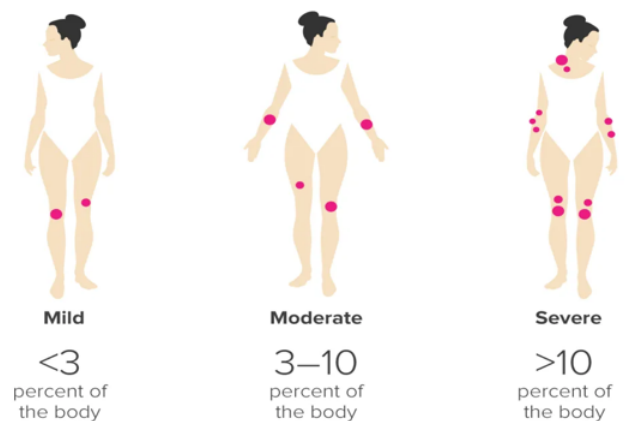
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Fig. 1: Psoriasis sites

Prevalence of psoriasis ranges between 0.5 to 4.7%. It can occur at any age. Symptoms often begins between ages 15 and 25, but is most common in the age group 50–69. Children account for 4.4% patients. Male to female ratio is 1:2.5. Most of the data is derived from hospital based studies.³ 25% of people with psoriasis could be classified as having moderate to severe psoriasis. Nearly

30% have arthritic problems. In people who have skin psoriasis 10–55 have psoriasis of nails. There is genetic susceptibility to psoriasis, 40% of patients have positive family history. HLA-Cw6 is implicated gene. Up to 60% of patients describe stress as being a key “exacerbator” or trigger of their disease.⁴ Precipitating factors for psoriasis are stress (upregulation of catecholamines), 2.5 times more in smokers, higher prolactin levels, Obesity (adipocyte proliferation), infection, trauma and drugs like B-blockers, lithium and antimalarials often show correlation.

1.1. Cytokines storm and Psoriasis

The clinical features of psoriasis, such as the hyperproliferation of keratinocytes, increased neovascularization and inflammation, and that by determining which cytokines played a central role in the disease process, interesting therapeutic targets could be identified (Figure 2a).⁵ In the time since, drugs targeting tumor necrosis factor (TNF)- α , interleukin (IL)-12/23, IL-17, IL-22, IL-23, granulocyte monocyte-colony stimulating factor (GM-CSF), as well as inhibitors of the Janus kinases (JAK1/2/3) downstream of a number of cytokine receptors. (Figure 2b)

The importance of type I IFNs in the triggering of psoriasis is strengthened by the well-documented induction of new-onset psoriasis or exacerbation of pre-existing psoriasis during treatment with IFN- α 2. Psoriasis lesions have long been known to contain elevated levels of IFN- γ , mostly secreted by skin T cells. IFN- γ contributes to the cytokine storm in psoriasis by, aiding and abetting other cytokines, in particular, IL-17, as well as playing a role in priming APCs, which drives IL-1/IL-23 production to augment Th17 responses Figure 3.⁵

1.2. Optimising therapies for Psoriasis

2. Using Topical Approach

First line management of adult mild-to-moderate adult plaque psoriasis is with topical treatment, including vitamin D analogues and topical corticosteroids. Topical therapies are indicated for patients whose affected area is < 10% of the body surface area. Topical vitamin D analogues and topical steroids are both widely used topical treatments. Calcipotriol, a vitamin D3 analog, acts not only to inhibit cell proliferation and enhance cell differentiation in the skin of patients with psoriasis, but also appears to have effects on immunologic markers that are thought to play a role in the etiology of the disease. Lower-potency corticosteroids are particularly recommended to apply on the face, groin, axillary areas, and in infants and children, whereas mid- and higher-potency corticosteroids are commonly used as initial therapy on all other areas in adults. Superpotent corticosteroids are mainly used for stubborn, cutaneous plaques or lesions on the palms, soles, and/or scalp.

Topical corticosteroids can aid in the treatment of psoriasis by:

1. Reducing inflammation
2. Slowing the hyperproduction of skin cells
3. Reducing the appearance of psoriatic skin lesions
4. Alleviating itching and discomfort
5. Aiding the shedding of scaly skin

Systemic retinoids are known to have immunosuppressive and anti-inflammatory activity and to modulate epidermal proliferation and differentiation. Tazarotene and acitretin are the only retinoids that are available in both topical and systemic formulations

Acitretin is an oral retinoid used in the treatment of extensive and severe refractory forms of psoriasis and Pustulous psoriasis of the hands and feet. Because of the potential for problems and severe side effects it is generally used in only very severe cases of psoriasis that have been unresponsive to other treatments. Acitretin is highly teratogenic and noted for the possibility of severe birth defects.

Tazarotene is a third-generation topical retinoid available as a cream, gel, and foam. Tazarotene properties are similar to that of Vitamin. In the treatment of psoriasis, it may be used in a combination with a corticosteroid cream or ointment, calcipotriol or phototherapy.

Methotexate orally helps psoriasis by decreasing the production of skin cells and suppressing inflammation. It may also slow the progression of psoriatic arthritis in some people. Methotexate is generally well tolerated in low doses. MTX is indicated as a systemic treatment in moderate to severe plaque psoriasis, psoriatic erythroderma, generalized pustular psoriasis, nail psoriasis, palmoplantar psoriasis, and, especially, in psoriatic arthritis. It is a good therapeutic choice for the treatment of psoriasis that has failed to respond to topical therapies, acitretin, broadband and narrowband psoralen-UV-A (PUVA) and UV-B, or when these therapies are unavailable or have been rejected by the patient.^{5,6}

Cyclosporine suppresses the immune system and is similar to methotexate in effectiveness. It induces immunosuppression through preventing down-stream T-cell activation. It inhibits the activation of Nuclear factor of activated T-cells (NFAT) & further inhibition of gene transcription of IL-2 by T cells. Cyclosporine can effectively treat severe and disabling psoriasis, and it works quickly. In clinical trials, 80% to 90% of patients who received cyclosporine for 12 to 16 weeks had rapid improvement.⁷

Mofetil (MMF) has higher efficiency than methotexate and cyclosporine in the treatment of psoriasis. MMF requires monitoring as it varied side effects. MMF may represent a good alternative for the treatment of psoriasis in patients who are unable to take MTX or other available

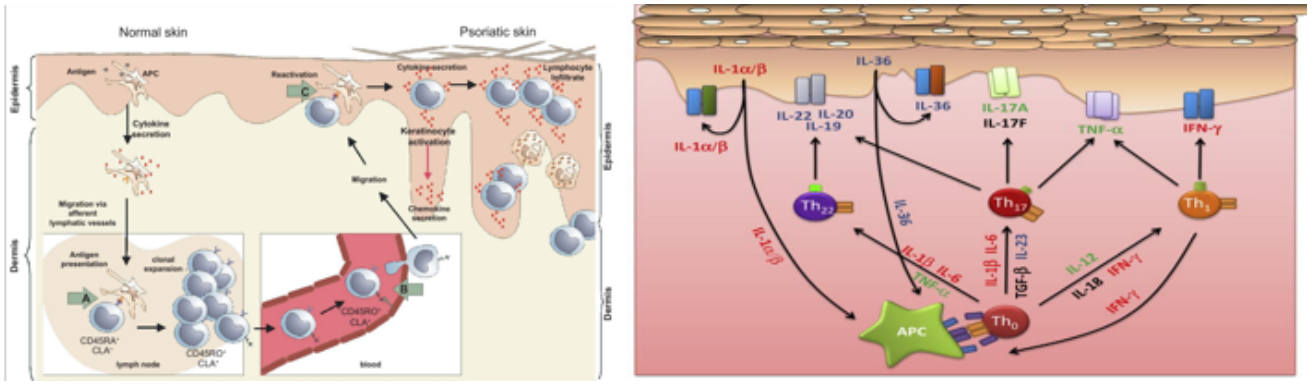


Fig. 2: a: cellular changes in psoriasis b: Cellular intercepts

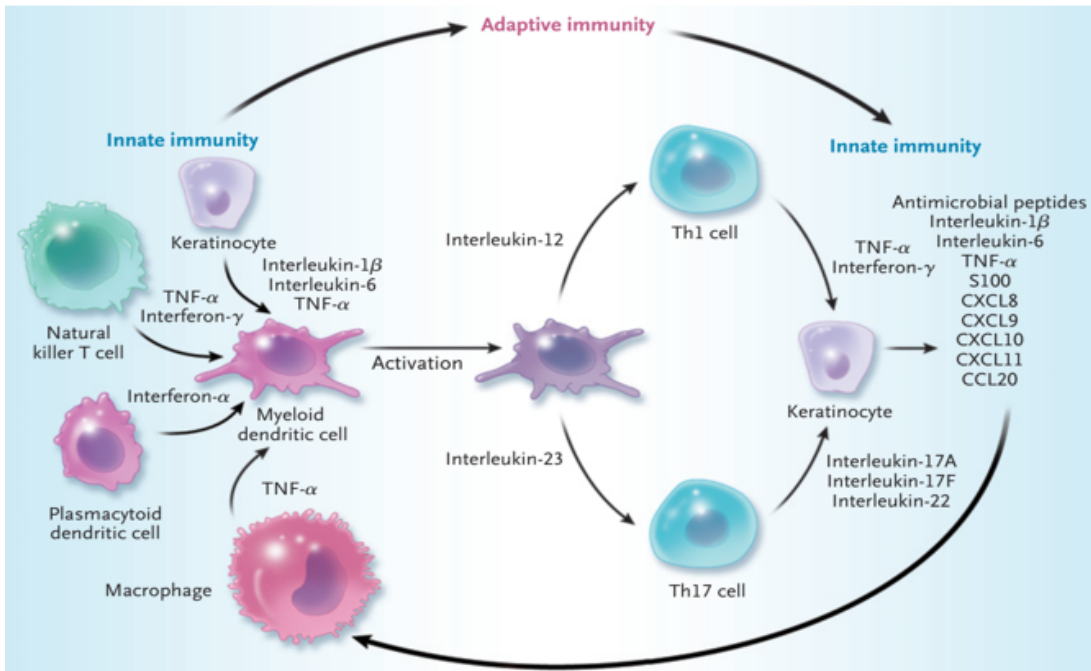


Fig. 3:

drugs due to contraindication or toxicity.

Tacrolimus mode of action is inhibiting the production of interleukin-2. Topical tacrolimus is particularly effective for inverse psoriasis, which is likely to be due to the reduced level of induration seen in these psoriatic lesions, which allows greater skin penetration, compared with hyperkeratotic plaques of psoriasis on the body. It is also notable that the areas affected by inverse psoriasis are more susceptible to adverse effects of topical corticosteroid therapy. Topical tacrolimus is prescribed off-license for the treatment of psoriasis,

Dimethylfumarate and/or monomethylfumarate: it is thought to involve a reduction in the production of inflammatory cytokines, promoting apoptosis, inhibiting keratinocyte proliferation, reducing expression of adhesion

molecules and lowering inflammatory infiltrate in psoriatic plaques. Dimethyl fumarate is used for the treatment of moderate to severe plaque psoriasis in adults when systemic treatment is indicated. NICE’s technology appraisal concluded that dimethyl fumarate improves severe psoriasis more than placebo but indirect comparisons suggest it is less effective than systemic biological therapies and apremilast

Anthralin (Dithranol) reduces keratinocyte proliferation, prevents T cell activation, and restores cell differentiation, probably through mitochondrial dysfunction. It cannot be used on the face or genitalia. Short contact anthralin therapy (SCAT) is advocated for the treatment of localized, scaly plaques of psoriasis. Side effects include a local burning sensation and irritation

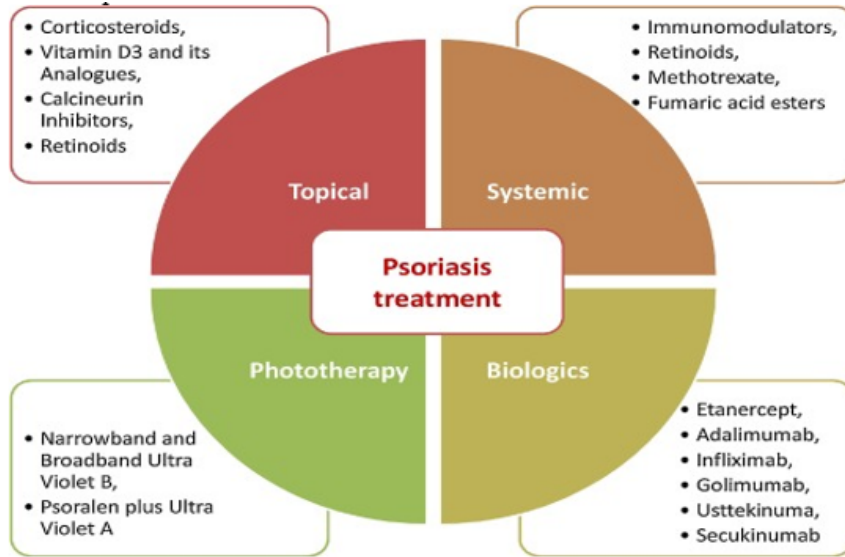


Fig. 4: Treatment options in Psoriasis

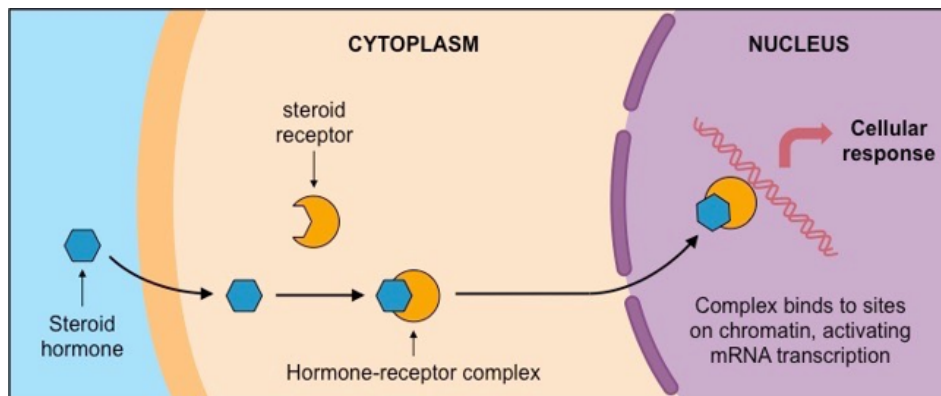


Fig. 5: Molecular action of steroid

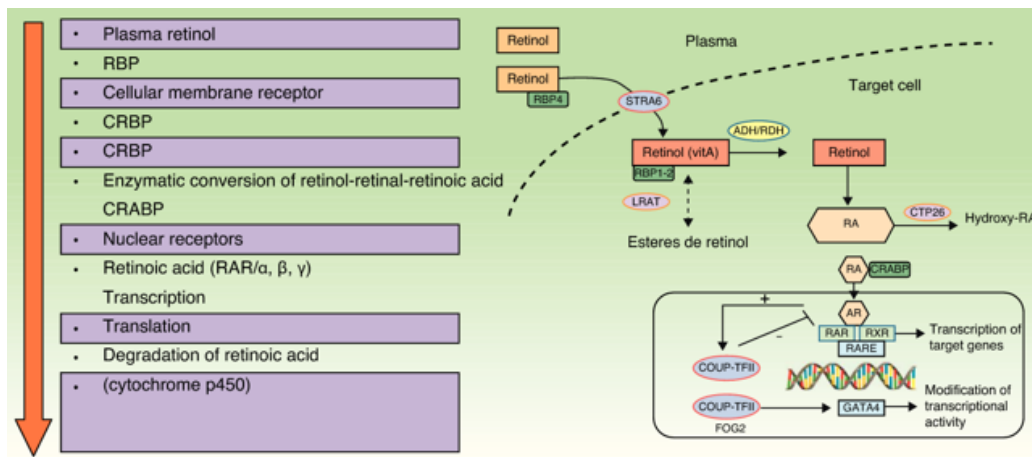


Fig. 6: Action of Retinoic acid

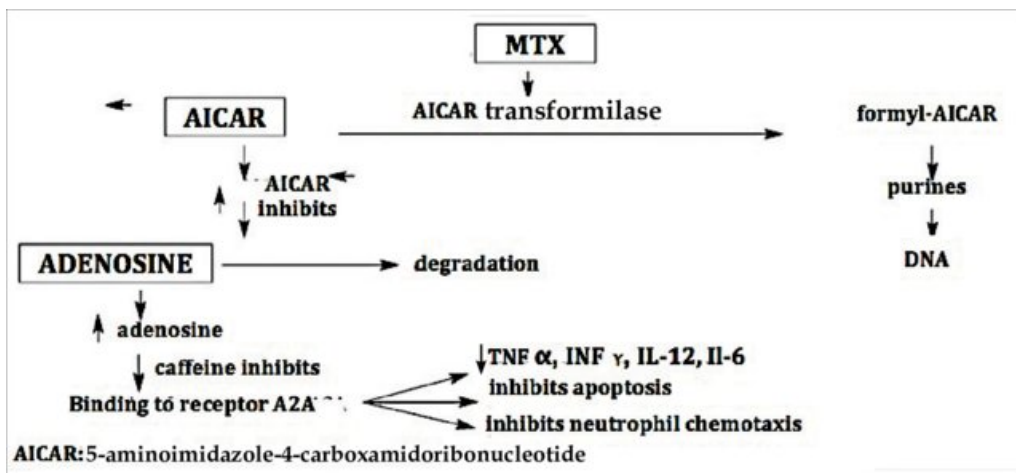


Fig. 7: Methotrexate action

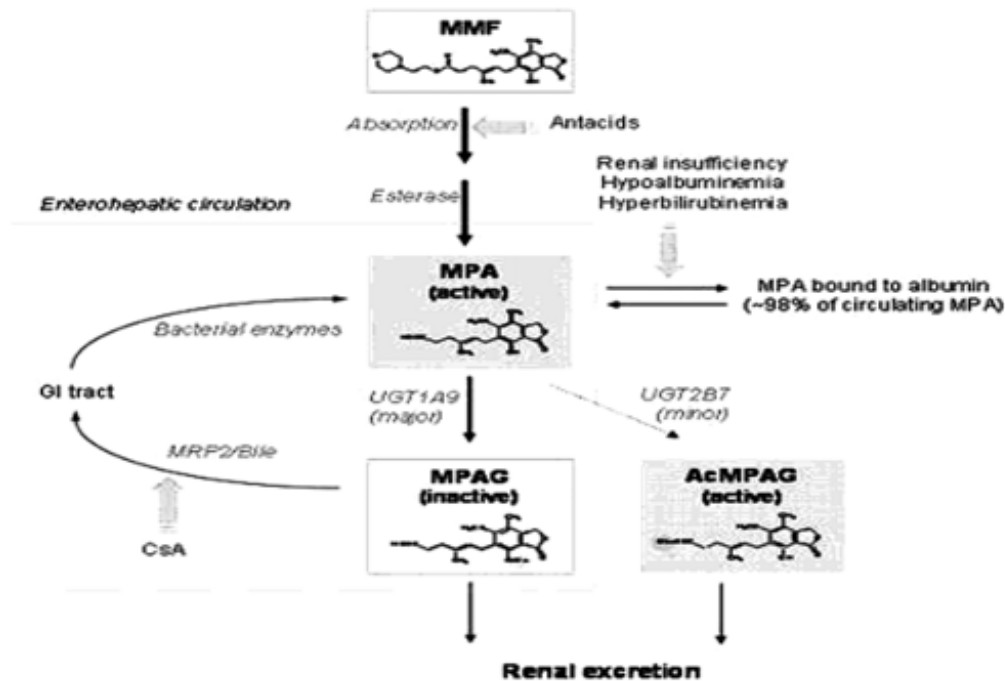


Fig. 8: MMF action

Tar preparations are helpful to remove loose scales of the patches of psoriasis. It is the first-line treatment for scalp, hand, and foot psoriasis. Tar preparations are available in the form of creams or ointments or shampoos. The mechanism of action of coal tar is not well understood. Postulated effects include a suppression of deoxyribonucleic acid (DNA) synthesis and subsequent inhibition of keratinocyte proliferation. Coal tar is thought to help correct the defect of differentiation in keratinocytes of patients with psoriasis.

Apremilast is an orally administered, small molecule inhibitor of phosphodiesterase 4 (PDE4). (Figure 4) Apremilast 30 mg twice daily reduced the severity of moderate to severe plaque psoriasis in the phase 3 ESTEEM trials, as well as improving difficult-to-treat nail, scalp and palmoplantar psoriasis. [6 a,b]

Light therapy: UVB exposure reduces the rate of DNA synthesis. In addition, UVB radiation causes photoisomerization of trans-UCA to cis-UCA which has immunosuppressive effects.

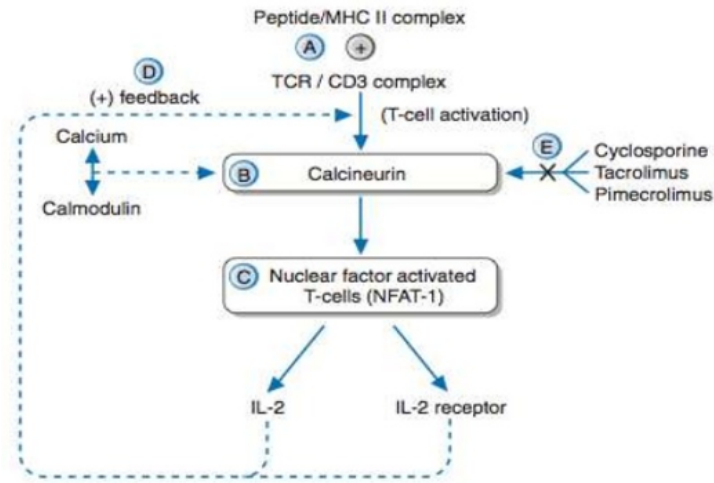


Fig. 9: Actions of Tacrolimus and Cyclosporine

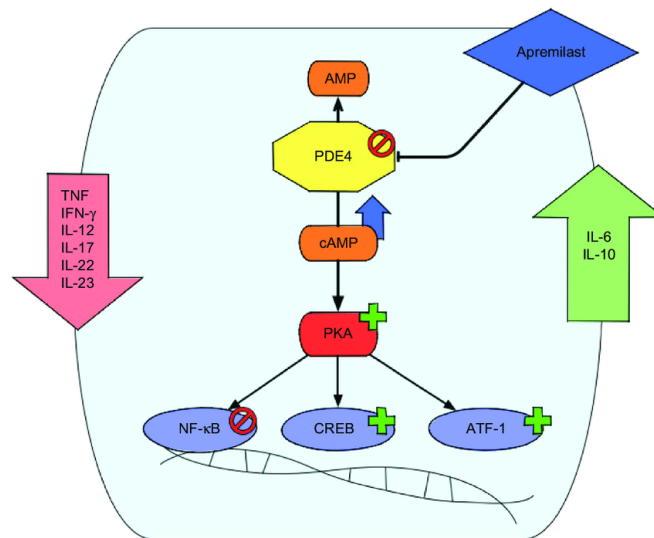


Fig. 10: Mode of Apremilast

Photochemotherapy or PUVA: has been found to be effective in psoriasis in well-conducted studies and randomized controlled trials. Psoralen derivative most widely used in PUVA is 8MOP (methoxsalen). Psoralens enter the cells and intercalate between DNA base pairs. On exposure to UVA, psoralens absorb photons, become chemically activated and covalently bind to DNA base pairs forming crosslinks. The DNA crosslinks have antiproliferative, antiangiogenic, apoptotic, and immunosuppressive effects. It is a relatively safe modality for the treatment of psoriasis, which is a chronic disease with remissions and relapses. Indications of PUVA are:

1. Psoriasis involving >20% body surface area
2. Unresponsiveness to topical therapy

3. Localized psoriasis of hands and feet (hand/foot unit)
4. Localized disease not responding to other modalities of therapy

The most significant complication of PUVA therapy for psoriasis is squamous cell cancer. Two carcinogenic components of the therapy include the nonionizing radiation of UVA light as well as the psoralen intercalation with DNA. Both processes negatively contribute to genome instability.⁸⁻¹²

Line of therapy in Psoriasis: Clinicians should be aware of the risk for nonadherence as they design and initiate treatment plans. Treatment options for patients with psoriasis depend first on disease severity. Topicals and phototherapy are first line for mild to moderate disease.

For moderate to severe disease, addition of systemic agents such as methotrexate, cyclosporine, or acitretin; small-molecular-weight immunomodulators such as apremilast; or biologic medications should be considered. Current biologics available for moderate to severe plaque psoriasis target TNF- α , IL-12/IL-23, IL-23, IL-17A, or IL-17A receptor.¹³

3. Usage of Biologics in Psoriasis

The ideal therapy for psoriasis is an efficacious, long-lasting agent devoid of acute or long-term adverse effects, with minimal monitoring requirements, and a dosing regimen that eases compliance. There is no cure for psoriasis. Biologic agent has been shown to induce periods of remission in patients with moderate-to-severe psoriasis. Clinicians must carefully screen patients to assess whether they are suitable candidates for biologic agents. Prior to initiating therapy with any biologic agent, appropriate screening studies include TB testing, complete blood count (CBC), hepatic function panel, hepatitis profile, and pregnancy testing as required.

Biologic agents for psoriasis have been proven to offer patients an effective alternative therapy for moderate-to-severe psoriasis.

The mechanistic design of each of the biologics is based on one of four general strategies:

1. Reduction of the pathogenic T-cells
2. Inhibition of T-cell activation
3. Cytokine mediated immune deviation from a T-helper (Th) type 1 to a Th2 response
4. Blocking the activity of inflammatory cytokines

Biological drugs are less toxic to the body and more effective than traditional therapies. Thus, they should improve the quality of life of patients with psoriasis. The long term side effect of the biologics is still being defined.^{14,15}

However, despite the high efficacy of these biologics, 20% to 30% of patients remain insufficient responders or non-responders. Improving the response rate of patients to treatment requires the appropriate selection of biologics.

3.1. The network meta analysis of drugs used in Psoriasis have shown following^{16–22}

1. Biologics can cause side effects, but they tend to be less severe. The most common side effects are minor irritation, redness, pain, or a reaction at the site of injection
2. The biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha showed significant superiority compared with small molecules and the conventional systemic agents, with small molecules

achieving better results than conventional systemic agents.

3. All of the anti-IL17 agents and the anti-IL23 guselkumab were significantly more effective than all of the anti-TNF alpha agents except for certolizumab (i.e. infliximab, adalimumab, and etanercept), and the anti-IL12/23 ustekinumab was superior to the anti-TNF alpha etanercept.
4. When compared with placebo, in order of highest efficacy, the following biological agents are the best choices: ixekizumab (high-certainty evidence), secukinumab (high-certainty evidence), brodalumab (moderate-certainty evidence), guselkumab (moderate-certainty evidence), certolizumab (moderate-certainty evidence), and ustekinumab (high-certainty evidence).
5. Tofacitinib was superior to methotrexate, and no difference was shown between the other small molecules and the conventional drugs.²³
6. Risankizumab, an anti-interleukin-23 monoclonal antibody, achieved significantly ($P < 0.001$) greater Psoriasis Area and Severity Index (PASI) and static Physician Global Assessment (sPGA) clear or almost clear (0/1) responses than adalimumab in a phase III trial in patients with moderate-to-severe psoriasis.²⁴

Natural Treatment for Psoriasis

Psoriasis symptoms can be relieved by change in diet and life style. Fasting food period, low energy diet and vegetarian diets have improved psoriasis symptoms. In some treatments supplemented with fish oil shows a beneficial effect due to the presence of omega - 3 Fatty Acids and Vitamin E. Natural supplements or herbs used in psoriasis are supplement for healthy skin, they may augment actions of drugs used in psoriasis.²⁵

Psoriasis algorithm recommended in Chronic Plaque Psoriasis > 5 % BSA without Psoriatic arthritis (Chart 1)²⁶:

Combination Therapy: Combination, rotational, and sequential approaches are often more effective and safer than single-agent therapy. Synergistic enhancement is seen with most paired combinations of the four major therapies: acitretin, phototherapy (ultraviolet B/psoralen plus ultraviolet A), cyclosporine, and methotrexate. The new biologic agents may prove to be important adjuncts in combination/rotational/sequential approaches. The need for combination therapy in patients with moderate-to-severe psoriasis is obvious, and combined treatment with retinoid and phototherapy is the only well-documented combination regimen for this disease. Severe cases, however, may warrant the use of short term combination therapy with a biological agent and phototherapy or a cytostatic in order to achieve remission, followed by maintenance therapy with biological monotherapy.^{27,28}

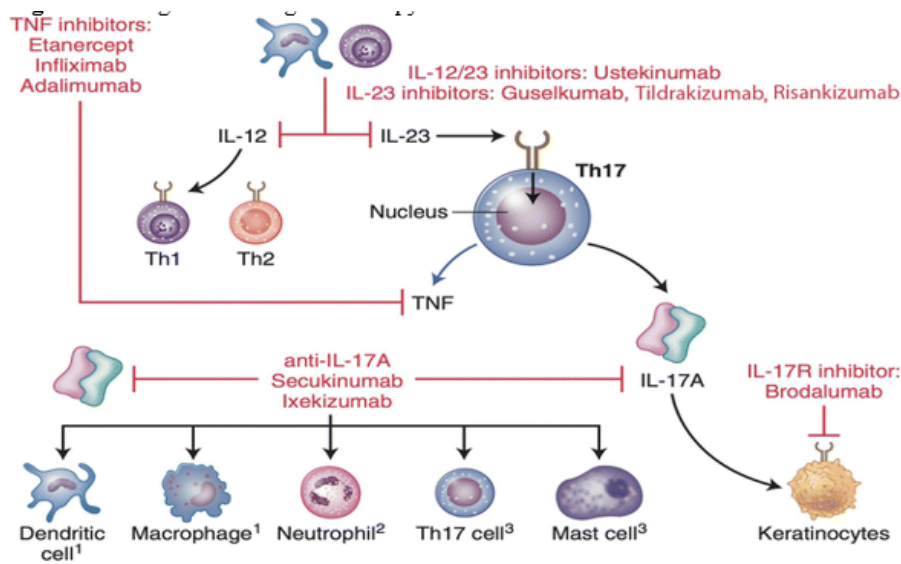


Fig. 11: Targets of Biological Therapy in Psoriasis

Table 1: Indications of Biological Therapy in Psoriasis

Severe disease defined as a “psoriasis area severity index (PASI)” score of 10 or more. (or a BSA of 10% or greater where PASI is not applicable) and “dermatological life quality index” >10	Are unresponsive to standard systemic therapy
Where phototherapy has failed or is contraindicated or the safe exposure limits of ultraviolet A (UVA) and ultraviolet B have been exceeded	Have severe, unstable, life; threatening disease.
Are intolerant to standard systemic therapy	Have significant coexistent comorbidity which precludes use of systemic agents
In patients where there is significant functional or psychological morbidity, they can be a first-line indication.	

Table 2: Indications to cease Biological Therapy in Psoriasis.

Failure to achieve an adequate response following treatment initiation or when treatment response is not maintained	Pregnancy (temporary withdrawal)
A serious adverse event such as malignancy (excluding nonmelanoma skin cancer), severe drug related toxicity, and severe intercurrent infection (temporary withdrawal)	Elective surgical procedures

Table 3: Anti TNF Agents

Class	Drug	Action
TNF- α inhibitors	Etanercept	It is used for the treatment of plaque psoriasis in adults and chronic plaque psoriasis in chil- dren. It is contraindicated in heart failure.
TNF - α inhibitors	Adalimumab	It is a monoclonal antibody. Its mechanism of action involves binding with host ligands and thereby prevention of interaction with TNF receptor, used in plaque psoriasis, psoriatic arthri- tis, and nail psoriasis.
TNF - α inhibitors	Infliximab	It is also a monoclonal antibody, used in psoriatic arthritis and chronic plaque psoriasis. It is associated with the risk of infection and malignancy.

Table 4:

Drug	Clinical Activity	Dose
Infliximab	50 weeks: 61% of patients = PASI-75	IV route , induction Weeks 0, 2, 6 = 5 mg/kg, maintenance Every 8 weeks = 5 mg/kg
Adalimumab	60 weeks: 68% of patients = PASI-75	SC route , Induction Week 0 = 80 mg, Week 1 = 40 mg, Maintenance Every 2 weeks = 40 mg
Etanercept	59% of patients = PASI-75	SC route , Induction Months 0-2 = 50 mg twice weekly Maintenance Every week = 50 mg
PASI	PASI score is a tool used to measure the severity and extent of psoriasis.	PASI 75 means that the person’s PASI score dropped by 75 percent as a result of the psoriasis treatment.

Table 5: Anti-interleukin

Class	Drug	Action
IL-12/IL-23 inhibitors	Ustekinumab	It acts against both IL-23 and IL-12, used for psoriatic arthritis and plaque psoriasis. Its dosing is weight-based.
IL-17 Inhibitors	Secukinumab	It is an IgG monoclonal antibody. It is typically used in severe scalp psoriasis and psoriatic arthritis. Contraindicated in patients with inflammatory bowel disease.
IL-17 Inhibitors	Ixekizumab	It acts by inhibiting the interaction of cytokine with its target receptor, used in the treatment of plaque psoriasis and psoriatic arthritis.
IL-17 Inhibitors	Brodalumab	It is indicated for plaque psoriasis. It is often associated with suicidal behaviour.
Selective IL-23 Inhibitors	Guselkumab	Its mechanism of action involves the binding of the p19 subunit of IL-23. It is particularly used for the treatment of psoriasis in adults.

Table 6:

Drug	Clinical Activity	Dose
Ustekinumab	PASI 75 = 67, Superior to etanercept, PASI 90 = 42	45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks
Secukinumab	PASI 75 = 82 PASI 90 = 59 Superior to ustekinumab, etanercept	the current approved dosing regimen is 300 mg subcutaneous at weeks 0, 1, 2, 3, and 4, followed by monthly maintenance dosing starting at week 8
Ixekizumab	PASI 75 = 90 PASI 90 = 71 Superior to ustekinumab, etanercept	Recommended dose is 160 mg (two 80 mg injections) at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks.
Brodalumab	PASI 75 = 86 PASI 90 = NA Superior to ustekinumab	Administer 210 mg of Brodalumab subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks
Guselkumab	At week 12, 50% (10 mg), 60% (30 and 100 mg), and 100% (300 mg) of guselkumab-treated patients, respectively, achieved a 75% improvement in PASI scores from baseline compared with 0% of placebo-treated patients.	100 mg administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter

Table 7: Anti TCell Strategies

Class	Drug	Action
Direction to T Cell	Efalizumab	Inhibits the binding of LFA-1 (Lymphocyte Function Associated Antigen) to intercellular adhesion molecule-1 (ICAM-1), thereby inhibiting the adhesion of leukocytes to other cell types.
Direction to T Cell	Alefacept	Blocks the interaction between the leukocyte-function-associated antigen (LFA)-3 and CD2 and thereby impedes the activation and proliferation of T cells

Table 8:

Drug	Clinical Activity	Dose
Efalizumab	PASI75 after 9–12 weeks: ~40%. Efalizumab has reproducibly proven its ability to rapidly and effectively control symptoms of moderate-to-severe plaque psoriasis	2 mg/kg weekly sc with/without topical steroid
Alefacept	PASI 75 was achieved in 28% of the patients and a PASI 50 in 56% of the alefacept-treated patients during treatment and follow-up control after the first course.	weekly intravenous (i.v.) 7.5 mg administration as well as intramuscular (i.m.) 15 mg injection.

* Data for all biologicals is from single sample study. There is no head to head comparison

Table 9:

Natural Source	Action
Capsicum annuum	Capsaicin stimulates the release of SP by binding to the vanilloid receptor on slow - conducting, unmyelinated type C neurons and ultimately leads to its depletion
Aloe vera	The Aloe group showed significantly higher rates of clearing the psoriatic plaques in almost all patients.
Silybum marianum	Silymarin in the treatment of psoriasis may be due to its ability to improve endotoxin removal by the liver, inhibit cAMP phosphodiesterase and inhibit leukotriene synthesis.
Angelica sinensis	This Chinese herbal medicine extracts contain potent furocoumarin i.e. psoralen. Psoralens are potent photosensitizers in the presence of UVA.
Matricaria recutita	The rationale for its use in psoriasis is that chamazulene, a by-product of the non – volatile oil extract, matricin, known to have anti – inflammatory activity by inhibition of lipoxygenase and as a result, leukotriene B4 (LTB4) formation.
Silybum marianum	The importance of silymarin in the treatment of psoriasis may be due to its ability to improve endotoxin removal by the liver, inhibit cAMP phosphodiesterase and inhibit leukotriene synthesis.
Alpinia galangal and Annona squamosa	They reported the molecular role of the extracts in suppressing psoriasis via regulation of NF-kB signalling biomarkers.
Ulmus rubra	Psoriasis area and Severity Index averaged post test scores showed significant improvement
Curcuma longa	Decreases in keratinocyte transferrin receptor expression and density of epidermal CD8 + T cells.
Nigella sativa	This was equivalent to the effect of the standard positive control, tazarotene (0.1%) gel
Wrightia tinctoria	showed significant antipsoriatic effect on mouse test model,
Olive Oil	Decreases cutaneous proliferation
Soyabean	Reduces inflammation by inhibition of pro-inflammatory cytokines, such as nuclear factor kappa B and STAT3

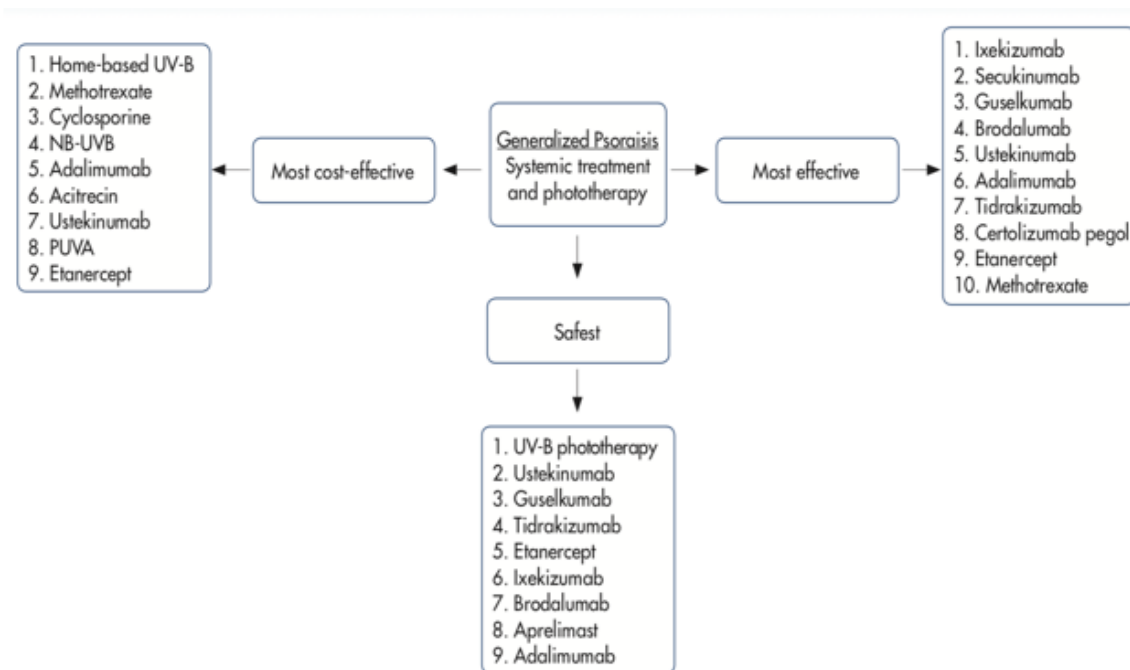


Chart 1:

4. Conclusion

Nearly half of individuals with psoriasis over the age of 65. Psoriasis generally does not affect survival but has significant detrimental effect on quality of life (QOL). The primary cause of psoriasis remains unknown. Abnormal epidermal cell kinetics and abnormal activation of immune mechanisms are thought to be the major contributors. The underlying immunopathology of psoriasis is correlated with the altered regulation of various cytokines such as TNF α , IL-23 and IL-17. The available therapies only relieve the symptoms. The choice of treatment is absolutely based on the type and severity of the disease. In patients who do not respond adequately to traditional topical treatments, oral and systemic agents are prescribed. Psoriasis is also associated with an array of important medical and psychiatric comorbidities that require timely therapy to improve long-term outcomes. The role of insulin resistance in the pathogenesis of psoriasis is under investigation.

5. Conflict of Interest

None.

6. Source of Funding

None.

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