Psoriasis: A Review of Existing Therapies and Recent Advances in Treatment

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Abstract
Psoriasis is a chronic autoimmune and non-communicable inflammatory disease of skin and joints. Antigen presenting cells activate naïve T cells, which further differentiate into Th1, Th2, and Th17 cells secreting cytokines like IFN-α, TNF-α, IL-2, IL-12 and IL-23 responsible for the pathogenesis of psoriasis. The therapies currently available ameliorate the progression and suppress the symptoms of the disease but there is no complete cure for the disease. This article has reviewed all the existing drugs used in the treatment of psoriasis. With better understanding of the immune-pathogenesis, the aim of therapy has now shifted to more selective, immunologically directed intervention. This paper describes an array of target based therapies like biologics which target the cytokine mediators and their receptors resulting into more specific and better therapeutic outcome. Immuno-pathogenesis has been described in detail along with all the approved biologics acting on various steps of pathogenesis cascade and the promising ones in various phases of trials for the treatment of moderate to severe psoriasis.

Keywords: Psoriasis, biologics, immunotherapy

INTRODUCTION
Psoriasis is a chronic autoimmune and non-communicable inflammatory disease of skin and joints. The word psoriasis comes from a Greek word “Psora” which means being itchy and “iasis” means a condition.1 The disease has a worldwide prevalence of two percent, with a higher prevalence of about 4.6% in developed countries.2

It is characterized by having sharply demarcated scaly, red, coin-sized skin lesions most often on the elbows, knees, scalp, hands and feet. Symptoms include itching, irritation, stinging and pain. Rarely, the entire skin surface of the body may be involved.3 Signs to diagnose psoriasis are koebner phenomenon4 and Auspitz’s sign.5

Etiology of this chronic condition is
not clear. Stress is the most common etiological factor and patients with chronic disorders like Crohn’s disease are more likely to suffer from psoriasis.\textsuperscript{6,7} Drugs that appear to have a strong causal relationship to psoriasis are beta-blockers, lithium, synthetic antimalarials, nonsteroidal anti-inflammatory drugs (NSAIDs), and tetracyclines.\textsuperscript{8} Patients with severe form of this disease have an increased risk of cardiac co-morbidities.\textsuperscript{9}

In this review, we briefly discuss about the immunopathogenesis followed by the existing therapies for the treatment of psoriasis. In addition, the review focuses on the newer target based therapies. The biologics which are currently approved for psoriasis by FDA and few which are still in pipeline to be approved, have also been reviewed.

**PATHOPHYSIOLOGY**

The pathophysiology of this chronic inflammatory disease is mostly unclear, but it is seen that dendritic cells or Antigen Presenting Cells (APC) sense stress signals generated by keratinocytes when antigen comes in contact with them. This further activates naïve T cells resulting in the secretion of various cytokines that allows further differentiation of naïve T cells into effector cells like Th1, Th2, and Th17. Now, each differentiated effector cell secretes cytokines like interferon (IFN-$\alpha$), tumor necrosis factor (TNF-$\alpha$) and interleukin (IL-2).\textsuperscript{10}

The differentiation of naïve T cells into Th1 and Th17 cells depends on the presence of two different cytokines IL-12 and IL-23, respectively. Th1 cells facilitate the secretion of TNF-$\alpha$, IFN-$\alpha$ and IL-2. These in turn activate APC to secrete more signals and activate more T cells.\textsuperscript{11,12,13} Th17 cells secrete IL-17, which is a prime cytokine in the pathogenesis of psoriasis and IL-23 promotes the expression of IL-17A, IL-17F and IL-22 by Th17 cells.\textsuperscript{14,15}

TNF-$\alpha$ binds to its receptor on the keratinocyte that activates the hyperproliferation resulting in the development of lesions. It also activates numerous cytokines and adhesion molecules involved in this inflammatory response.\textsuperscript{16} Recent reports from inflammatory skin models suggest that IL-23 plays a crucial role in the pathogenesis of psoriasis and helps in differentiation into Th17 T cells, which produce IL-17 and IL-22. These cytokines seems to be pivotal inducers of epidermal hyperplasia resulting in abnormal maturation and epidermal differentiation in psoriasis.\textsuperscript{17} Psoriatic plaques shows high level of vascular endothelial growth factor which promotes angiogenesis and results into bleeding points when peeled off (Auspitz’s sign).\textsuperscript{5} IL-8 has been shown to be responsible for the accumulation of neutrophils in the skin.\textsuperscript{18}

**ASSESSMENT OF SEVERITY**

Psoriasis Activity and Severity Index (PASI) is the most commonly used tool to assess the severity of psoriasis and psoriatic arthritis. Scoring is done at baseline and after the treatment. The PASI quantifies and assesses the extent of body surface involved and the severity of desquamation, erythema and plaque induration (thickness) in each region, yielding an overall score of 0 (no psoriasis) to 72 (severe psoriasis).\textsuperscript{19} PASI 75 is defined as a 75% reduction in PASI compared with baseline.
EXISTING THERAPIES

There is an array of topical and systemic drug therapies and the treatment regimens should be optimized in such way so as to achieve optimal compliance and benefit. Treatment goals for each patient is customized on the basis of concomitant co-morbidities, adverse effects, existing quality of life, self-care capability, drug history, caregiver situation, financial needs and feasibility for follow up. Treatment is usually started with the economical therapies and then escalated to newer / costlier ones until an acceptable and effective therapy is reached with good compliance. The treatment modalities are as follows:20

1. **Corticosteroids** – They are the most frequently prescribed medications for treating mild to moderate psoriasis. They slow cell turnover by suppressing the immune system, which reduces inflammation and itching. Low-potency corticosteroid ointments are usually recommended for sensitive areas such as face or skin folds, and for treating widespread patches of damaged skin. Adverse effects seen are thinning of the skin, telangiectasia and systemic side effects such as diabetes, hypertension and HPA suppression. Some of the corticosteroids used are clobetasol propionate 0.05%, amcinonide 0.1%, betamethasone dipropionate, betamethasone valerate as 0.1%, 0.12% and 1%, halcinonide 0.1%, desoximetasone 0.25% and mometasone furoate.21

2. **Vitamin D Analogues** – Vitamin D analogues (calcitriol and calcipotriene) have emerged as important alternatives to topical corticosteroids for the long-term therapy of psoriasis. They bind to cytoplasmic Vitamin D Receptor then translocate into the nucleus, where they bind to nuclear receptor and commence the transcription of vitamin D responsive genes. These transcription proteins then regulate cell differentiation and down regulate cell proliferation and inflammatory processes associated with this condition. They are considered a safe alternative, despite causing peri-lesional irritation and erythema. They may rarely increase serum and urine calcium levels, so the total concentration per week should not exceed 100 gm. Calcitriol is more potent analogue but calcipotriene is most established one. Calcipotriene has shown to affect calcium homeostasis to very lesser extent.22 Most trials have shown that combination treatment of vitamin D and corticosteroid was usually more effective than monotherapy with either used alone.23

3. **Anthralin (Dithranol)** – It is derived from the Araroba tree found in South America. It induces reactive oxygen species release, which has an inhibitory effect on hyper proliferating keratinocytes and the transformation of leucocytes. It is used in increasing concentrations (0.1% to 3%) for application to the scalp. It can be applied on in-patient basis; also out-patient short-contact therapies are now available. Adverse effects are discoloration of the hair and skin irritation.24 Few studies have shown the use of anthralin when combined topical therapies or phototherapy has improved response.25
4. Coal Tar – It is one of the oldest topical therapies used both as monotherapy and in combination with other topical agents, systemic agents and phototherapy for the treatment of psoriasis. The polycyclic aromatic hydrocarbons present in coal tar makes the skin more sensitive to UV light.\textsuperscript{25} Still the exact mechanism of action is unclear. Coal tar has anti-inflammatory, anti-proliferative and strong anti-pruritic properties.\textsuperscript{26} Its unpleasant smell, staining properties and mutagenic potential has made it less compliant. In order to increase the compliance, some non-staining and washable formulations including lotions and shampoos are available either alone or in combination with other active agents.\textsuperscript{27}

5. Retinoids – Oral retinoids are mainly used as maintenance therapy in chronic plaque psoriasis and very specifically used in pustular psoriasis and can also be used in erythrodermic psoriasis but it seems to be less efficacious.\textsuperscript{28} It is believed to normalize DNA activity in skin cells and may minimize inflammation. The prescribed daily dose is 10–50 mg per day, which can be given as a single dose or in divided doses. Adverse effects of retinoids are a major concern and can include skin irritation, increased sensitivity to sunlight, xerosis, pruritus, cheilitis, alopecia, xerostomia, dyslipidaemia, deranged liver enzymes and teratogenicity. A low dose regimen is also an option where up to 25 mg per day is given to minimize mucocutaneous side effects.\textsuperscript{27,28}

6. Methotrexate – This is an immuno suppressive, antimetabolite and is one of the most effective as well as relatively low-cost therapy to treat psoriasis. Methotrexate is dihydrofolate reductase inhibitor and folic acid is supplemented to decrease toxicity of the drug. It is usually given as a single oral dose per week. Adverse effects can be myelosuppression, mucositis, hepatotoxicity, pulmonary toxicity, nephrotoxicity, neurotoxicity, gastrointestinal upset, nausea, oligospermia, and teratogenicity.\textsuperscript{29,30} Long term therapy can cause hepatotoxicity that can progress to liver fibrosis.\textsuperscript{31}

7. Cyclosporine – It is very effective oral treatment option to treat moderate-to-severe psoriasis. It binds to cyclophilin, inhibits calcineurin, and hence 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.\textsuperscript{32} Adverse effects can be nephrotoxicity, hepatotoxicity, hypertension, diabetes mellitus, neurotoxicity, hirsutism, increased risk of infection and an increase in non-melanoma skin cancers with long-term use.\textsuperscript{33}

8. Phototherapy – It is recommended for those patients who do not respond to topical therapies or for patients with plaques of psoriasis covering 20% or more of the body surface. Though exact mechanism is not clear, but it is believed to induce apoptosis along with enhanced transcription and expression of IL-10 in keratinocytes. It has shown a good success rate with more than 80%
of the patients having skin clearance.\textsuperscript{34} Ultraviolet B (UVB) radiation combined with coal tar (Goeckerman therapy) or anthralin (Ingram regimen) has been seen to be effective in patients with moderate-to-severe psoriasis. Ultraviolet A radiation (UVA) combined with systemic psoralens (PUVA therapy) has been seen to be highly effective in clearing skin lesions, but both these therapies require a maintenance treatment and they increase the risk of skin cancer.\textsuperscript{35} Narrowband UVB therapy (311-313 nm) is more effective than broadband UVB treatment. It is administered 2 to 3 times a week until the skin improves, then maintenance may require only weekly sessions. It may cause more severe and longer lasting burns. When given in combination with topical tazarotene, it is almost equally efficacious and safer alternative to PUVA.\textsuperscript{36,37} Adverse effects are redness, itching, dry skin, wrinkled skin, freckles & skin cancer.

NEW DRUG TARGETS

In the past two decades the interest has shifted towards the pathogenesis based treatment which has led to development of novel biologics. These therapies aim at providing more selective, immunologically directed intervention, with a hope that such specificity will result in fewer side effects than traditional therapies. As this is an era of target-based therapies, the development of the new drugs and biologics are based on following strategies:\textsuperscript{38}

1. Blockade of initial cytokine release and APC migration
2. Targeting activated T cells and prevent further T-cell activation and immunological cascade
3. Inhibition of cytokines such as TNF $\alpha$
4. Inhibition of differentiation of the activated T cells into Th1 and Th17 cells
5. Inhibition of cytokines like IL-17 and its interaction with the receptor

BIOLOGICS

These are the molecules, which are developed for target-based therapy. They have a more precise action and side effects are thought to be less as compared to the broad traditional therapies. These agents act on the varied steps of the pathogenesis of the psoriasis and are divided into various groups on the basis of their mode of action.

ANTI TNF-$\alpha$ AGENTS

These are molecules, which act on the tumor necrosis factor (TNF-$\alpha$) or by blocking the TNF-$\alpha$ receptors. Psoriatic plaques contain a high amount of TNF-$\alpha$ which is a strong pro-inflammatory cytokine and is one of the prime mediators in the development of inflammation in psoriasis. TNF-$\alpha$ stimulates the production of other cytokines, activates other immune cells and increases its own secretion and also induces the adhesion of molecules by keratinocytes and further increases the recruitment of immune cells.\textsuperscript{38} Hence, anti TNF-$\alpha$ agents binds to TNF-$\alpha$, captures them and finally neutralizes them or blocks the TNF-$\alpha$ receptor on the keratinocytes and other immune cells to shut down the immunological cascade. The first biologic in this group is Infliximab. Other anti TNF-$\alpha$ agents which have been developed till now are Etanercept, Certolizumab pegol, Adalimumab, Golimumab.
Infliximab is a chimeric monoclonal antibody prepared by joining human immunoglobulin (IgG1) constant region to a murine-derived antigen-binding variable region.\(^3^9\) Infliximab has high affinity for both soluble and transmembrane-bound forms of TNF-\(\alpha\) and hence inhibits the ability of TNF-\(\alpha\) to bind to its receptors and initiate the intracellular signaling, which further leads to gene transcription and subsequent inflammatory cascade.\(^4^0,4^1\) The recommended dosage is 5 mg/kg body weight as IV infusion at 0, 2 and 6 weeks followed by every 8 weeks thereafter. First three infusions are to be given under supervision, as there are high chances of infusion reactions. Other adverse effects can be development of anti-nuclear antibody and rarely, a lupus-like syndrome. It is also approved for indications like rheumatoid arthritis (RA), Crohn’s disease, ulcerative colitis (UC), and ankylosing spondylitis (AS).

Etanercept is a recombinant human TNF-\(\alpha\) receptor fusion protein which neutralizes soluble TNF-\(\alpha\) and is in the use for moderate to severe psoriasis\(^4^2\). Recommended dosage is 50 mg subcutaneously twice weekly for the first three months and thereafter followed by 50 mg weekly. Contraindications to therapy are multiple sclerosis, congestive heart failure (CHF), immunosuppression, hepatitis B. It is also approved for RA and AS.

Certolizumab pegol is a recombinant, humanized anti-TNF-\(\alpha\) antibody. It is administered subcutaneously as 400 mg taken at week 0, week 2, week 4, then every 2 weeks thereafter. Adverse effects are T.B, CHF, lupus-like syndrome, hepatitis B reactivation, easy bruising.

Adalimumab is a fully humanized monoclonal antibody IgG1 and is produced to capture the TNF-\(\alpha\). It is administered subcutaneously as 40 mg once weekly every other week. Better efficacy than infliximab & etanercept has been seen in some studies. Contraindications to therapy are multiple sclerosis, CHF, immunosuppression, hepatitis B. Malignancy rate is also seen to be lower.\(^4^3\)

Golimumab is a fully humanized monoclonal antibody IgG1 and it captures and blocks TNF-\(\alpha\). It is administered subcutaneously as 50 mg once a month.\(^4^4\) Adverse effects are increased risk of infection, T.B, bruising & bleeding, CHF, lymphoma, lupus-like syndrome, hepatotoxicity.\(^4^4\)

**IL-23 AND IL-12 INHIBITORS**

Th17 cells and IL-23 are important in the pathogenesis of psoriasis. IL-23 stimulates the immune cells and increases their proliferation and survival. Dendritic cells and macrophages increase the production of IL-23 and are important for the development and maintenance of Th17 cells. These IL-23 and IL-12 inhibitors like Ustekinumab and Apilimod block the subunits of IL-23 and IL-12 and hence ceases the immunological cascade.\(^1^8,4^5\)

**Ustekinumab** – It is a humanized monoclonal antibody directed against p40, a subunit of IL-23 and IL-12 and inhibits their signal-transduction pathways that normally promote the differentiation of naïve T cells into Th1 and Th17 cells respectively.\(^4^6\) The treatment is started with 45mg (or 90mg if >100kg) at weeks 0 and 4 and every 12 weeks thereafter. The clinical trial data shows a comparable PASI 75 response of adalimumab and ustekinumab\(^4^7,4^8,4^9\) and a head-to-head study with etanercept.
showed a more favorable PASI response of ustekinumab compared to etanercept. It has been recently approved for Crohn’s disease.

**Guselkumab** – It is a human monoclonal IgG1\(\alpha\) antibody that selectively binds to the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor. It has shown to reduce serum levels of IL-17A, IL-17F and IL-22 relative to pre-treatment levels in evaluated subjects with psoriasis. The recommended dose is subcutaneous injection of 100 mg at Week 0, Week 4, and every 8 weeks thereafter. This biologic has been approved this year for the treatment of adults with moderate-to-severe plaque psoriasis.\(^50\)

**Apilimod** – It is a novel triazine derivative which was developed and identified through a high-throughput IL-12 inhibitor screening.\(^51\) Recent literature search suggests that apilimod not only suppresses the synthesis of IL-12 and IL-23 but also suppresses multiple downstream cytokines in the lesional skin and also concomitantly increases synthesis of the anti-inflammatory cytokine IL-10.\(^52\)

**IL-17 A RECEPTOR INHIBITOR**

Brodalumab is a monoclonal antibody that targets interleukin-17RA, blocks signaling of interleukins 17A and 17F and also the interleukin-17A/F heterodimer, hence blocking the downstream pathways, all of which play a role in the inflammatory cascade of psoriasis.\(^53\) Recently FDA approved brodalumab for treatment of moderate-to-severe plaque psoriasis. The week 12 PASI 100 response rates were significantly higher with 210 mg of brodalumab than with ustekinumab but neutropenia was higher than with ustekinumab.\(^54\) A dose of 210 mg is administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks. FDA has issued warning regarding increased risk of suicidal ideation and behavior.

**IL-17 A INHIBITORS** – Secukinumab and Ixekizumab are monoclonal antibodies that have been developed to target and specifically neutralize interleukin\(^17\). Interleukins associated with the Th17 pathway play a crucial role in the pathogenesis of psoriasis.

**Secukinumab** – This is another novel biologic therapy for moderate-to-severe psoriasis. Head on trials with etanercept have concluded that it is more efficacious than etanercept.\(^55\) The dosage is 300 mg/dose subcutaneous injection once a week for first five weeks, then every four weeks thereafter. Adverse effects can be nasopharyngitis, headache, diarrhea, upper respiratory tract infections and rarely, neutropenia.

Ixekizumab is a humanized IgG monoclonal antibody that neutralizes interleukin-17A. FDA has approved it to treat adults with moderate-to-severe plaque psoriasis. It is administered subcutaneously in patients with chronic moderate-to-severe plaque psoriasis with a dosage starting with 160 mg first dose then 80 mg every two weeks.\(^56,57\)

**FUSION PROTEIN INHIBITOR**

Alefacept is the drug in this group, which is approved by FDA. It is a human fusion protein and it binds to CD2 on T cells. It has dual mechanism of action, it blocks the interaction between the leukocyte-function-associated antigen (LFA)-3 and CD2 on T cells and hence blocks the activation and
proliferation of the immune CD4+ and CD8+ T cells. It also induces apoptosis of activated memory T cell.\textsuperscript{58} Dosage is 15 mg IM or 7.5 mg IV per week and adverse effects can be lymphopenia, skin cancers, lymphomas, hepatotoxicity.

**JANUS KINASE (JAK) INHIBITOR**

Tofacitinib is an oral selective Janus kinase inhibitor that was approved by FDA for the treatment of rheumatoid arthritis (RA) but recently it is being studied and is in phase 3 trials for the treatment of psoriasis. Tofacitinib selectively inhibits signaling by blocking JAK3 and JAK1 with more selectivity than the receptors that functions through JAK2.\textsuperscript{59} JAK1 inhibition results in decrease in signaling by additional pro-inflammatory cytokines, such as IL-6 and IFN-\(\alpha\). In addition, it also inhibits IL-23 signaling by suppression of IL-23 receptor expression, resulting in inhibition of immune cells like Th17 cell differentiation.\textsuperscript{60,61}

**PHOSPHODIESTERASE-4 INHIBITOR**

Phosphodiesterase 4 (PDE4) is an enzyme that is responsible for the hydrolysis of cyclic adenosine monophosphate (cAMP), which is an intracellular second messenger that controls a group of pro-inflammatory and anti-inflammatory mediators.

Apremilast is an oral drug that has been approved by FDA for psoriatic arthritis and moderate to severe plaque psoriasis. It works intracellularly to regulate inflammatory mediators by increasing the cAMP levels in the cells, including pathways, which

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Figure 1: Figure summarizing the pathogenesis, existing therapies and target of various and therapies is treatment of psoriasis.
are responsible for the pathogenesis of psoriasis. Adverse effects are diarrhea, nausea, upper respiratory infections, headache and weight loss.

**ANTI CD-6 (CLUSTER OF DIFFERENTIATION) MONOCLONAL ANTIBODY**

Itolizumab is a drug which blocks the signaling and differentiation of T cells into Th1 and Th17. Pre-clinical studies have also shown that it inhibits the intracellular phosphoproteins like mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription-3 (STAT-3), which are involved in intracellular signaling pathways as triggered by CD6. It has been seen that STAT-3 is also responsible in production of Th17. It has also been found to down regulate the gene transcription of pro-inflammatory cytokines and cell adhesion molecules. Ultimately it leads to decreased levels of IFN-α, IL-6, and TNF-α, leading to reduction in the immune T-cell infiltration at the sites of inflammation and psoriatic plaque formation. It is administered as I.V. infusion with a recommended dosage of 1.6 mg/kg once every 2 weeks for 12 weeks and 1.6 mg/kg once in four weeks until 24 weeks. Adverse effects can be infusion reaction, URI, urinary tract infection (UTI), lymphopenia. It is still not approved by FDA.

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CONCLUSION

We have a lot of treatment options for psoriasis but no cure for psoriasis has been found till date. 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. These treatments depend on the patient's general health, age, co-morbidities, form and severity. Most of the drugs, especially the newer ones, require close monitoring for the potential adverse effects.

Table 1 summarizes all the existing therapy and the novel biologics.

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REFERENCES


