Psoriasis: History, Present and Future Prospects

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Abstract
Psoriasis is a chronic condition which causes the inflammation of the skin due to the activation of immune system leading to abnormal keratinocytes proliferation. The keratinocytes mature within a week as compared to normal cycle of 27 to 28 days. The oldest of the treatment includes the use of coal tar, Dithranol, sunlight, Dead Sea salts and emollients. Dermatologists now have a host of new treatments for psoriasis, using immunobiologics to combat this disease. The first line treatment includes topical therapy with corticosteroids and phototherapy treatment. Immunomodulators have been use as an option for second line treatment, but most of them as off label therapies. The potent candidates include calcineurin inhibitors and cytotoxic agents. Methotrexate is considered as a gold standard against which the efficacies of other biologics are being evaluated. Novel drug delivery systems are also on their way for the treatment like methotrexate niosomal gel.

Keywords: psoriasis, corticosteroids, biological agents, calcineurin inhibitors, immunosuppressants

Introduction
Psoriasis is one of the most common skin diseases affecting both men and women. The word has been derived from Greek word psora meaning itch. Psoriasis is not a contagious disease as it looks like. Psoriasis is mainly an autoimmune disease in which body’s own immune system leads to excessive proliferation of keratinocytes. Recent findings indicate the involvement of cell mediated immune system in the epidemiology of psoriasis. The excessive proliferation leads to physical characteristics involving multilayered, thickened silver colored, scaling plaques. The squamous keratinocytes in psoriasis release very less amount of extracellular lipids which play an important role in adhesion of corneocytes, which results in scales and flakes. The active plaques are encircled by white vasoconstricted skin which results from local overproduction of prostaglandins. The disease has a much larger psychological impact which substantially affects the quality of life. Psoriasis is also associated with increased risk of many other diseases. At least 10% to 20% of the population suffering from psoriasis develops arthritis also known as psoriatic arthritis (1). The disorder is chronic and reoccurring which vary in severity in different genetically susceptible populations. An attempt has been made in the present manuscript to deliver information about the types of treatments available over the last few decades for the treatment of psoriasis. The disadvantages of the drugs used earlier that led to the development of newer strategies for treating psoriasis, have also been highlighted in the current article.

Epidemiology : The prevalence of psoriasis is almost equal in both the genders and is irrelevant of the age group. The most common occurrence is in the age of 15-35 years. 10-15 % of the cases have been diagnosed in children who are below
the age of 10 years of age (2). It has been rarely observed from birth. The mean age of occurrence is estimated to be 33 years. It affects mainly 3% population of America (25% having severe symptoms) and 2-3% in United Kingdom. The disease is most prevalent in Caucasians having a rate of 60 cases per 100000 in a year. The psoriasis has least occurrence in African and Asian countries with least value of 0.1%. China has only 0.3% occurrence of psoriasis among total population. The least prevalence has been found in some ethnic groups of Japan and Indian natives from South America (3).

Psoriasis and psoriatic arthritis are ailments with genetic components as well. In the genetic analysis of patients suffering with psoriasis, many susceptibility loci have been identified in the recent findings. Family studies on genetic basis provide sufficient evidence that psoriasis have a strong genetic basis. In case of twins, the probability in monozygotic twins was 62-70% as compared for 21-23% dizygotic twins (4). The major gene locus PSORS1 has been mapped on chromosome 6p21.3 and is mainly responsible showing susceptibility to psoriasis and psoriasis arthritis.

Environmental factors have shown their direct effect in induction of psoriasis along with the quality of life geographically. A large number of endogenous and exogenous factors contribute to psoriasis such as stress, trauma, injury, infections, smoking, drugs and many more. Higher rates of incidence have been found in eastern Africans than in western Africans. It has been demonstrated by the fact that western Africans lack the main susceptibility loci as compared to eastern Africans. The regions having high humidity have recorded low cases of psoriasis as compared to dry hot areas. Low incidence of psoriasis have been observed in people having diet rich in proteins and low in carbohydrates such as the population of Canada, Greenland and Siberia (5).

Pathogenesis: Today psoriasis comes under the category of most prevalent autoimmune disease occurring due to inappropriate and unwanted activation of cellular immune system. Human skin is a primary lymphoid organ which is well equipped with keratinocytes, endothelial cells, epidermal T cells, different macrophages, draining nodal cells and other cells which form a part of human immune system. In case of psoriasis, an unknown antigen causes the Antigen Presenting Cells to activate in the epidermis resulting in whole cascade of inflammation. The maximum T-lymphocyte infiltration includes CD4+ in the dermis region and CD8+ in the epidermis region (3). The adhesion molecules which are responsible for leukocyte adherence and inflammatory pathway are expressed at higher levels in psoriasis. The activated T cells increases secretion of mRNA for interleukins (IL2), resulting in increased synthesis of IL-2 receptors as well. The cytokine production is also elevated, which includes TNFα, IFN-Ω, IL-4, IL-10 and IL-11, each down regulating and modifying others responses. The up regulation of the genes, which code for vascular endothelial growth factor increases vascularization and angiogenesis which is observed in psoriasis (Fig.1). The inflammatory response of body alters the normal epidermal cycle of 28 days to 2-4 days, leading to scaly plaques.

Types of Psoriasis: The severity, location, and appearance of psoriasis depend on the kind of psoriasis a person has. Plague psoriasis is the most common and widely spread form of psoriasis. The patches in psoriasis may appear as small red spots or may be in the form of scales and patches. Psoriasis has been classified into pustular and non pustular depending upon the presence of pustules. In pustular psoriasis, white blood cells are present in pus present in blisters. Guttue and inverse psoriasis have least occurrence among all types of psoriasis.

Novel Drug Delivery Approach for Psoriasis: The topical route always remains the first choice for producing a local effect. A survey reported that about 70% of the patients remain unsatisfied with the treatment from conventional dosage forms and other routes of administration (40). So, novel
Fig. 1. Overview of the processes involved in the activation of immune system in psoriasis and the drug targets.

Table 1. Various types of psoriasis as defined clinically

<table>
<thead>
<tr>
<th>Type of Psoriasis</th>
<th>Description</th>
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<tbody>
<tr>
<td>Pustular (3,6): Pustular psoriasis appears as raised eruptions which consist of non infectious pus.</td>
<td>Von Zumbusch or Generalized pustular psoriasis</td>
</tr>
<tr>
<td>Non pustular (3,6) : In non pustular there are no signs of pustules or eruptions.</td>
<td>Inverse psoriasis or flexural psoriasis</td>
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<td>Scalp psoriasis</td>
</tr>
</tbody>
</table>
Therapeutic agents and Formulations | Information regarding therapeutic agents | Adverse drug reactions and contradictions.
--- | --- | ---
**Arsenic**: Argue drops, Fowler’s solution and Asiatic pills (7) | Arsenic was used as a sulphide derivative in paste form for skin disorders. A tasteless formulation of arsenic known as Argue drops was preached. | Arsenic poisoning, nerve injury and cancer

**Ammoniated Mercury**: Ammoniated mercury ointment | Ammoniated mercury was used as an ointment. Mercury salts were best suited for psoriasis of palms and soles. Now days it is occasionally prescribed due to cases of heavy metal poisoning and skin deposition (7). | Mercury poisoning, skin rashes. Contraindicated with sulphur and iodine.

**Anthralin derivatives**: Ingram regimen | Anthralin (Dianthrone) was used as a bright yellow cream. The structure activity relationship of Anthralin was used to develop new derivatives like hydroxyl anthrones. The patients, treated were wrapped in stockings for about 24 hours and the procedure was repeated every day. | Local irritation, burning and staining Contraindicated in hypersensitivity and eruptive psoriasis.

**Salicylic acid**: Creams, ointments and cleansing soaps | Topically used 2-3 times a day earlier in the form of a paste but now a day’s it is available as shampoos and lotions which are FDA approved for psoriasis (8). Salicylic acid acts by loosening and softening the keratinocytes and thus easy to remove scales. | Irritation, itching, peeling, redness, Folliculitis and salicylism. Contraindicated with other topical skin care products like Tretinoin.

**Coal tar**: Scytera®, Oxicom VHC® psoriasis lotion. | The treatment includes application of coal tar in the evening, allowing it to remain throughout the night and then removed next day. Coal tar was used individually or in combination with UV light. Tars consist of high benzene content and aromatic hydrocarbons which have carcinogenic potential (9). | Skin irritation, acne type eruptions and increased sensitization to sunlight. Contraindicated in pregnancy.

**Dead sea salts** | It includes bathing in sea water having high concentration of salts of mineral origin. These salts reduce the activation of T cells in the skin (10). This treatment is also termed as Balneo therapy and Climato therapy. | Sensitivity reactions to mineral salts, promote skin allergy and ageing. Contraindicated in pregnancy, hypertension, and tuberculosis.

**Tazarotene**: Tazorac cream and gel (0.1%) | Tazarotene contains a chemical similar to vitamin A which slows cell proliferation. It belongs to a wide class known as retinoids. Tazarotene is a prodrug of tazarotenic acid which is a receptor selective acetylenic retinoid (1, 11). It is most commonly prescribed in concentrations of 0.05% and 0.1%. | Bleeding, cracks in skin, dry skin irritation, skin discoloration. Contraindicated in skin cancer and especially pregnancy.

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**Table 2. Various agents used before 19th century**

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<table>
<thead>
<tr>
<th>Therapeutic agents and Formulations</th>
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<th>Adverse drug reactions and contradictions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Geokerman regimen</strong></td>
<td>The therapy consists of application of coal tar, followed by exposure of skin to UV light. Coal tar is applied to the patient once or twice a day and skin was exposed to UVB radiation. It minimized the time of application of tar and amount.</td>
<td>Sunburn, freckling, and skin aging. Contraindicated in patients with tar sensitivity and Thrombophlebitis</td>
</tr>
<tr>
<td><strong>Topical and oral steroids:</strong></td>
<td>The corticosteroids directly affect the immune response by preventing phospholipids release required as a primary precursor in synthesis of inflammatory mediators. Corticosteroids prevent the sequestration of CD4+ T-lymphocytes and prevent proliferation by inhibiting cytokines and lymphokines (12). Other mechanisms include inhibition of delayed hypersensitivity, antigen processing and inhibition of IL-2. The steroids have been classified in seven classes according to the potency and vasoconstricting properties. The Class I steroids are considered to be of highest potency (clobetasol propionate). Class VII indicates the lowest level of potency (hydrocortisone). A major problem with this therapy is that, the reemergence of the disease occurs if the treatment is stopped.</td>
<td>Skin atrophy, stretch marks, Prolonged use leads to Cushing’s syndrome.</td>
</tr>
<tr>
<td>Betamethasone valerate (Betnovate® cream/ointment)</td>
<td>Hydroxyurea: Hydrea®(oral)</td>
<td>Bone marrow toxicity, Neutropenia and leucopenia. Contraindicated in anemia and blood disorders.</td>
</tr>
<tr>
<td>Clobetasol propionate (Etrivex shampoo®)</td>
<td>Hydroxyurea: It was first recommended for psoriasis in 1960. Hydroxyurea is an antimetabolite used for treating chronic leukemia and cancer of cervix. The active form is converted into nitro oxide radical who selectively inhibits DNA synthesis in proliferating cells (12, 13). It is preferably recommended when other systemic agents like cyclosporine have failed.</td>
<td></td>
</tr>
<tr>
<td><strong>Fumaric acid esters:</strong></td>
<td>Fumaric acid esters: They are marketed as mixture of dimethylfumarate and zinc salts of monoethylhydrogen fumarate (1). The mechanism includes shifting of Th1 type cytokine receptors to Th2 type pattern and inhibiting translocation of nuclear factors required for genetic regulation of inflammatory factors.</td>
<td>Allergic sensitizer, GIT stress and kidney disturbances. Contraindicated in chronic gastrointestinal disease, kidney disease and abnormal hematology counts.</td>
</tr>
<tr>
<td>Psori care plus®, Fumaderm®</td>
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Table 3. Various agents used from 1920-1970
Phototherapy
A daily short non-burning exposure of sunlight has proved useful in treating psoriasis (14). UVB therapy includes a narrowband light source in which more than 83% of the UV rays is within the required range of 310-313 nm are considered to be most effective. Ultraviolet therapy having a range of 320-400nm along with a photo sensitizing agent such as 8-methoxy psoralen has been used for treating psoriasis (PUVA). Specific Excimer lasers which can produce a wavelength of 308 nm UVB provided localized effects (15).

Burning, skin tanning, skin cancer with prolonged exposure. Contraindicated in history of arsenic exposure, ionization radiation exposure and pregnancy.

Table 4. Various agents used from 1970 onwards

<table>
<thead>
<tr>
<th>Therapeutic agents and Formulations</th>
<th>Information regarding therapeutic agents</th>
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<tbody>
<tr>
<td>T-Cell inhibitors/ Calcineurin Inhibitors</td>
<td>Cyclosporine is an endogenous peptide used in chronic conditions orally. Cyclosporine acts by inhibiting calcineurin and another protein cyclophilin A, forming a high affinity complex. The complex formation inactivates calcium stimulated calcineurin, preventing further activation of DNA binding proteins inhibiting transcription of interleukins (16). It is basically used in chronic conditions orally having a dose of 3-5mg/kg for about 10-12 weeks. A decrease in PASI score by 70-72% was observed when Cyclosporin was used for treatment of psoriasis.</td>
<td>Nephrotoxicity, hypertension, elevated serum lipids, gingival hyperplasia paresthesias. Contraindicated during breast feeding and hypersensitivity.</td>
</tr>
<tr>
<td>Tacrolimus: Prograf®, Advagraf®, Protopic®.</td>
<td>Tacrolimus is a macrolide antibiotic, which acts by inhibiting T cell activation. It binds to an intracellular protein FKBP-12 by forming a transcriptionally active NF-AT complex with them, preventing the dephosphorylation and translocation of activated T cells (17). It also targets mast cells and impairs histamine release. The major metabolite of Tacrolimus is 13-demethylated derivative, but 31-demethylated derivative shows immuno-suppressive effect. The systemic administration of Tacrolimus is associated with high liver toxicity and Nephrotoxicity, so topical application have been preferred</td>
<td>Nephrotoxicity, GIT upset, hypertension, insomniac conditions. Tacrolimus ointment is not approved for use in children. Contraindicated in pregnancy and pre-existing hypertension.</td>
</tr>
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</table>
### Pimecrolimus: Elidel®

Pimecrolimus, another macrolide derivative which binds to macrophillin-12 (FKBP-12) and inhibits calcineurin, preventing T cell activation and cytokine release (18). It is more selective than Tacrolimus and has no effect on dendritic cells which carry out the process of antigen presentation. The drug is being evaluated clinically for psoriasis and has shown improvements in PASI score.

Lymph node and skin malignancy, herpes infections. Cream 1% is contraindicated in individuals with a history of hypersensitivity.

### Sirolimus: Rapamune®

It blocks T cell activation later by binding with mammalian target of Rapamycin (mTOR) protein (19). It differs from Tacrolimus as it does not interact with calcineurin. It also inhibits platelet derived growth factor (PGDF) in smooth muscle cells. It also decreases T cell response, antibody production and thymocyte proliferation.

Lung toxicity, tachycardia, GI disturbances, hyperlipidaemia, peripheral edema, hypertension leukopenia and angioedema. Contraindicated in pregnancy and lactation.

### Everolimus: Zortress®, Certican®, Afinitor®

Everolimus is 40-O-(2-hydroxyethyl) derivative of Rapamycin which is also an mTOR inhibitor. It has been approved for advanced kidney cancer and organ rejection but is under trial for psoriasis. Everolimus act specifically on mTOR protein, leading to hyper activation of kinase AKT via negative feed back loop mechanism of mTORc1. It has been observed in random controlled trials that the PASI score reduced to 60% after 4 weeks of therapy 3mg twice daily (20).

Back, arm or leg pain, constipation, diarrhea, dizziness, headache, loss of appetite, upset stomach, weakness, sleeping trouble. Contraindicated in lactating mothers and hypertension.

### Efalizumab: Raptiva®

Efalizumab is a recombinant humanized monoclonal antibody which binds directly to CD11a subunit of LFA-1. The binding of LFA-1 to ICAM is hindered preventing co-stimulation (21). The recognition of ICAM-1 which is expressed on dermal surface promotes firm adhesion and subsequent migration of T lymphocytes into the cutaneous area, which is hindered. Due to its adverse effects including multifocal leucoencephalopathy it was withdrawn from market globally in 2009.

Headache, pale skin, dark colored urine, confusion. Contraindicated in known hypersensitivity and clinically important infections.

### Infliximab (TNFá blocker): Remicade®

It is a chimeric monoclonal antibody (75% human+25% murine) which directly blocks TNFá. It neutralizes both soluble and membrane bound cytokines and lead to down

Pruritus, urticaria, dyspnoea, delayed hypersensitivity worsening heart.
<table>
<thead>
<tr>
<th><strong>Regimen</strong></th>
<th><strong>Details</strong></th>
<th><strong>Contraindications</strong></th>
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<tbody>
<tr>
<td>Infliximab</td>
<td>Regulation of IL-8. Infliximab is approved by FDA for psoriatic arthritis, moderate to severe plague psoriasis and Crohn’s disease (22, 23).</td>
<td>Failure. Contraindicated in active TB, moderate or severe CHF, severe infection, pregnancy and lactation.</td>
</tr>
<tr>
<td><strong>Adalimumab</strong>: Humira®</td>
<td>Adalimumab is an engineered fully human monoclonal antibody (24). It binds to membrane bound TNFα based on concentration before TNFα can bind to p55 and p75 surface receptors, inhibiting activity of cytokines. It has been administered along with phototherapy continuously or intermittently in patients with mild to severe psoriasis. It was approved in January 2008 for moderate to severe psoriasis.</td>
<td>Fatal blood disorders, re-occurrence of TB and associated infectious diseases.</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Human monoclonal antibody which is directed against IL-12 and IL-23. It binds to p40 subunit of the interleukins. IL-12 is a key cytokine that stimulates T cell differentiation (25). Ustekinumab has been approved in Canada, Europe and USA for psoriasis.</td>
<td>Increased risk of infections, brain swelling, allergic reactions.</td>
</tr>
<tr>
<td>Siplizumab</td>
<td>Siplizumab is also a human monoclonal antibody with human IgG1 kappa in combination with rat antihuman CD2 monoclonal antibody (26). It binds to a conformational isotope on human CD2 receptors in T lymphocytes and natural killer cells.</td>
<td>Lymphopenia, anemia, chills, nausea, increased risk to infections.</td>
</tr>
<tr>
<td><strong>Certolizumab, Golimumab, Briakinumab</strong></td>
<td>Certolizumab, a pegylated Fc free anti TNF antibody has high affinity to TNFα. Another antibody golimumab is under phase III trial (27). It is fully human anti TNF IgG monoclonal antibody having affinity for both soluble and trans-membrane TNF. Briakinumab is fully human monoclonal IgG1 antibody.</td>
<td>Worsening of CNS demyelinating disease, neurological disorders and hematological disorders. Contraindicated in pregnancy and breast feeding.</td>
</tr>
<tr>
<td><strong>Etanercept</strong>: Enbrel®</td>
<td>Etanercept is a recombinant human TNF receptor p75 fusion protein which binds to TNFα specifically. It competitively interferes in interaction of TNFα with its cell bound receptor and so inhibits effect of cytokines. It was approved by FDA in May 2004 for treatment of moderate to severe psoriasis (28, 29).</td>
<td>History of recurrent infections or risk of infection, respiratory tract and abdominal pain, lymphoma, CNS demyelinating disorders. Contraindicated...</td>
</tr>
<tr>
<td><strong>Alefacept:</strong> Amevive®</td>
<td>Alefacept is a fully human dimeric fusion protein, having extracellular CD2-binding portion of human leukocyte function antigen -3 (LFA-3) linked to Fc portion of IgG1 (30). It reduces the circulating level of T memory cells by binding to CD2. It also induces apoptosis in CD4 memory effector T cells. Alefacept was approved in May 2002 by FDA for treatment of psoriasis. It is being recommended that a prior CD4 lymphocyte count should be carried out before initiating therapy.</td>
<td>Mild swelling, Bleeding at the injection site, pharyngitis, cough, nausea, Pruritus, myalgias and hepatic toxicity. Contraindicated in known hypersensitivity to Alefacept and in HIV patients.</td>
</tr>
<tr>
<td><strong>Abatacept:</strong> Orencia®</td>
<td>It is recombinant fusion protein having extracellular domain of CTLA-4 which binds to CD80/86 receptor of APC (31). It inhibits the co-stimulation of T cells. The co stimulatory signal is generated by binding of T cell to B7 protein on Antigen Presenting Cells.</td>
<td>Chronic obstructive pulmonary disease (COPD), Signs of allergic reactions, including unexplained rashes. Concomitant Use with TNF Antagonists.</td>
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<tr>
<td><strong>Vitamin D analogues:</strong> (Modify cytokine expression) Calcipotriene (Dovonex®) Calcipotriol (Rocaltrol®) Calcitriol (Taclonex®)</td>
<td>Vitamin D analogues have shown to reduce the basic functioning of APC’s (32). D3 is a hormone that binds to vitamin D receptors (VDR) and regulates calcium metabolism, and cell proliferation. They modify Th2 cytokine expression along with decrease in IL8 and decrease in IL10. Vitamin D analogues also reduce transcription of IL2 by inhibiting nuclear factor-kappa B thus affecting genetic regulation of cells (33).</td>
<td>Pruritus, burning sensation, erythema, rashes, photosensitivity and hypersensitivity reactions. Contraindicated in suspected disorders of calcium metabolism, Patients with erythrodermic, exfoliative and pustular psoriasis.</td>
</tr>
<tr>
<td><strong>Retinoids</strong> (RAR receptor blocker) Acitretin (Soriatane® or Neotigason®)</td>
<td>Retinoids act directly by normalizing epidermal proliferation and cell differentiation. Acitretin is a FDA approved systemic and oral retinoid which has been used in combinations. Isotretinoin is a systemically active weak retinoid which is a metabolite of Acitretin (34).</td>
<td>Conjunctivitis, dry sore mouth, Hypervitaminosis A, hypercholesterolemia, benign intracranial hypertension; photosensitivity. Contraindicated in Pregnancy, lactation. Hepatic and renal impairment. Hyperlipidaemia.</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Methotrexate: Trexall®, Rheumatrex®.</td>
<td>Methotrexate is a synthetic analogue of folic acid which is a competitive inhibitor of enzyme dihydrofolate reductase, responsible for the conversion of dihydrofolate to tetrahydrofolate (35). So indirectly it inhibits the replication of T and B cells and suppresses cytokine secretion (IL-1, IFα and TNF±). Hepatotoxicity, Thrombocytopenia, GIT ulceration, Stomatitis, malaise, pulmonary toxicity. Contraindicated in Severe renal or bone marrow suppression and lactation.</td>
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<tr>
<td>Azathioprine:</td>
<td>Azathioprine is a synthetic analogue of purine bases which are incorporated in RNA and DNA (36). Oral Azathioprine is used for systemic therapy for severe psoriasis. Azathioprine is a prodrug of 6-mercaptopurine which is formed after metabolism. 6-MP is further anabolized via HPGRT pathway to a purine analog that inhibits DNA and RNA synthesis and repair leading to immunosuppression. Carcinogen, Myelosuppression, veno-occlusive liver disease, anorexia, arthralgias. Contraindicated in Hypersensitivity, previous treatment with alkylating agents, pregnancy and lactation.</td>
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<tr>
<td>Mycophenolate mofetil: CellCept®, Myfortic®, Baxmune®.</td>
<td>It was in 1995, mycophenolate mofetil received approval for prevention of acute renal grafts and as a treatment for immune mediated diseases. Currently it is under trials for psoriasis, but often used off-label. MMF non-competitively binds to enzyme inosine monophosphate dehydrogenase in de novo purine synthesis pathway which inhibits the purine synthesis, thus overall inhibiting genetic expression (17, 37). Hypomagnesaemia, hypocalcaemia, neoplasia, Myelosuppression. Extreme caution when MPA is used in patients with childbearing potential and in lactating mothers.</td>
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<tr>
<td>Others</td>
<td>Suphasalazine plays an important role in inflammatory bowel disease especially Crohn’s disease. The mechanism of action has not been established properly still it has been found to act upon 5- lipooxygenase (38). Paclitaxel is a chemotherapeutic agent which is recommended for breast and ovarian cancer. Due to its anti-inflammatory properties, it has been used at a dose of 75mg/m² every two weeks in psoriasis patients. Colchicine has shown leukocyte suppression, antimitotic and cell mediated immune response inhibition activity (39). It has been used against palmoplantar and pustular type psoriasis. Depression, infertility, thrombocytopenia, bone marrow suppression, Neutropenia, Hyperinhibition of mitosis.</td>
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Drug delivery always provides a better prospective in such cases. The base is to incorporate drug in specifically designed carriers which can provide specificity, act on target and reduce the side effects. The conventional dosage forms need to be incorporated in recent carrier systems to limit side effects of drugs.

Drug delivery to patients suffering from psoriasis need to be categorized in two categories:

- **Topical drug delivery** limited to skin to provide a local effect.
- **Drug delivery to body’s immune system** to limit its over expression

Drug carriers such as nanoparticles can be an effective option in delivery of drug topically and systemically. It has been proved that nanoparticles smaller than 10 nm can directly penetrate through intracellular route and enter systemic circulation where they are recognized by reticuloendothelial system. Non-stealth nanoparticles are considered foreign and internalized by phagocytosis, where they are acted upon by various enzymes leading to their breakdown and releasing drug eventually. Particles larger than 10 nm accumulate in the hair follicle openings, interact with skin lipids and release the drug slowly. The small particle size of the nanoparticles enables its close contact with the horny layer of the skin and increases the amount of encapsulated compounds penetrating into the skin.

Transferosomes, one of the recent carriers, have a capability to penetrate corneocytes junctions due to their ultra deformable nature. Delivery of proteins and biological molecules with transferosomes provides a successful way to deliver high molecular weight molecules to skin.

Apart from advantages, novel drug delivery system has disadvantages like high cost of excipients, expertise in production and stability issues. The state of the hydration of skin is one of the most prominent factors influencing drug absorption. In psoriasis, the rigidity of skin occurs due to high concentration of cholesterol and low level of moisturizing factors. Apart from this excessive growth, aberrant differentiation of corneocytes leads to alteration in absorption properties (41).

**Liposome and Transferosomes:** Transferosomes are highly deformable lipid carriers which can cross the skin barrier through intercellular pathways and can easily adapt during stress. Dexamethasone was approved by FDA in 1958 and mostly available in conventional formulations like topical sprays or ophthalmic drops. Earlier liposomes of corticosteroids have been prepared and reported but drug release has been found inconsistent. The preparation of corticosteroid loaded transferosomes showed spontaneous transport across the skin barrier better than other formulation. In vivo study of transferosomes of dexamethasone has shown to suppress ear edema than corresponding creams and topical formulations. The transferosomes of hydrocortisone and dexamethasone have showed faster onset, reduced drug abrasion and dose reduction, emerging as a potential carrier (42).

Dyphylline, a derivative of theophylline, inactivates cyclic AMP (cAMP), and therefore has been indicated in the treatment of psoriasis. An increase in dyphylline permeation has been observed across abdominal mice skin when liposomal delivery was targeted (43).

Temoporfin, a light sensitizer used in photodynamic therapy has been studied in the form of liposomal gels. Its poor aqueous solubility has limited its capacity for its topical delivery. Temoporfin loaded invasomes has showed positive results in topical delivery (40, 44).

An approved formulation for psoriasis known as Psorisome® Gel has also been formulated. Psorisome® is a novel liposomal formulation of Dithranol in gel base, which have enhanced drug application topically (45). The encapsulation of Dithranol in liposomes has reduced its irritant, burning and staining properties due to its oxidation during application. The micro carrier system provides a proper microenvironment and maintains hydration thus enhancing drug permeability.

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Nanoparticles and Nanostructured lipid carriers: Nanoparticles are stable colloidal particles consisting of biodegradable polymers or lipids as a vehicle for delivery of drugs which have a size range of about 10-1000 nm. Nanostructured lipid carriers (NLCs) are lipid carriers in which liquid lipids have been used for increasing entrapment of the drugs (46).

Tacrolimus which is calcineurin inhibitor shows high inter-subject pharmacokinetic variability due to narrow therapeutic index and close drug monitoring is required during its administration. PEG–PLGA nanoparticles of Tacrolimus have been prepared for reduction in the adverse effects of systemic Immunosuppression and simultaneously enhancement in immunosuppressive efficacy by selectively transferring Tacrolimus into the lymphatic system (46). The pegylation of Tacrolimus showed positive results in lymphatic targeting.

Acitretin loaded nanostructured lipid carriers have been formulated and evaluated. Oral Acitretin is widely indicated and accepted for chronic adult psoriasis, but the application is restricted due to its systemic side effects and teratogenicity. The utilization of Acitretin is limited due to several disadvantages such as skin irritation, very low water solubility and high instability in the presence of light, air and water. Formulating with a suitable carrier has shown to lessen systemic toxicity and increasing local bioavailability (47). The results have shown remarkable decrease in erythema, scaling and betterment of symptoms.

Cyclosporine, another pioneer in the treatment of psoriasis has shown to treat psoriasis both by topical and systemic effects. Earlier cyclosporine was formulated in an oily vehicle and administered orally for graft rejections leading to incomplete absorption varying 6-60% and high degree of Nephrotoxicity. Polymeric nanoparticles of cyclosporine have been prepared using Eudragit RL100 and in-vivo and in-vitro studies have been carried out. The nanoparticles were highly taken up by reticuloendothelial system and thus their localization in lymph nodes and bone marrow (40, 48).

A combination study of calcipotriol and methotrexate was studied in the form of nanostructured lipid carriers or topical delivery. Calcipotriol has severe skin irritation reactions and so its dose needed to be minimized. During their combination study in the form of NLCs using different concentrations of a lipid precirol, a larger flux of drug through skin was observed as compared to control. The combination confirmed that NLC systems are a promising carrier for the topical delivery of ant psoriatic drugs as revealed by enhanced skin permeation, negligible skin irritation, and the compatibility of the two drugs (49).

Niosomes: Methotrexate has been studied due to its poor permeation and solubility characteristics. Topical methotrexate niosomal gel has been prepared and its efficacy has been estimated in humans using a double-blind placebo controlled study (50). It has been observed that topically applied niosomes can increase the residence time of the drug and reduce systemic absorption. The niosomes form a lipid layer on the skin which prevents the subcutaneous inter and intracellular hydration.

Dithranol and coal tar have also been used in niosomal and lipid coated microparticles form. Dithranol has not been fully accepted because of staining and irritant properties as well as poor permeation (42, 51). Dithranol therapy includes long term exposure of skin for proper treatment. The local topical delivery of drug have increased bioavailability and reduced dose dependent effects. Dithranol entrapped in niosomal form have shown better permeation properties as compared to conventional formulation.

Microemulsions: Microemulsions modify the skin properties which affect the permeation characteristics of drug. 8-methoxsalen which belongs to a category of furocoumarins has been widely used. The bioavailability of methoxsalen

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is highly variable due to poor solubility and first pass effect (52, 53). Microemulsion formulations containing 8-methoxsalen have been prepared and studied. The results obtained suggested the enhanced promotion and localization of 8-methoxsalen into skin and long term effects have been obtained using microemulsions as vehicle. Other methods in drug delivery have been developed. Techniques such as iontophoresis, sonophoresis, alteration of skin permeability by mechanical perforation enhances the drug delivery of colloidal carriers (54). The improvement in topical delivery has been achieved by methods such as:

- Use of hydrogels and ointment basis for preventing transepidermal water loss.
- Disruption of stratum corneum using chemicals.
- Use of permeation enhancers in formulations.
- Enhancement of thermodynamic activity of drugs in formulations.

**Novel biological therapies and their status**

Apart from large number of therapies, cure has not been established for psoriasis. Since it is an immunological disorder, preference has been given in targeting bio-molecules which elicit the immune response. The biological agents have shown better targeting approach and higher clinical efficacy, as compared to other agents which have a large profile of adverse reactions. A large number of biological agents which were used in other immunological disorders are being evaluated clinically specifically in psoriatic conditions (Table 5). These synthetic proteins counteract one or more pathogenic pathway and specifically tackle various cytokine mediators (55,56). The biologicals have improved and better risk to efficacy ratio.

All of these novel drug delivery systems have provided better results than the conventional forms. Dithranol and coal tar gel is among the novel formulation that has been approved for psoriasis. Recent route of drug delivery includes transungual route which can be used to deliver medication in case of nail psoriasis. Till now no formulation have been approved for nail psoriasis but drugs incorporated and injected through suitable carriers can be used to administer drugs through nail plate. The stability of the formulations, their proper delivery techniques, proper safety profile and cost will be the targets to be achieved in the near future.

**Herbal Treatments and Natural Remedies**

The increasing resistance of newer therapies with immunosuppressants and antimetabolites still focuses the importance of natural and ayurvedic therapies in the treatment of psoriasis. Ayurvedic and Chinese herbal medicines have been used for centuries for the treatment of psoriasis. Herbal medicines involved in psoriasis involve *Psoralea corylifolia* (babchi), *Coleus forskohlii* and *Ammi visanga* (khella). Herbs such as aloe vera, ...
Chamomile, tea tree oil, turmeric, milk thistle, primrose oil, lavender, flaxseed oil, wintergreen oil, guggul and oregano oil have also found to be effective (1, 57). Psoraban® is an ayurvedic product which mainly reduces hyper proliferation and inflammation. This indicates that herbal treatments can offer safe, effective and inexpensive treatment for psoriasis.

**Co-morbidities Associated with Psoriasis:**

Data collected all over the world have suggested the association of various co-morbidities with moderate to severe psoriasis. Co-morbidities like metabolic syndrome, cardiovascular diseases, Crohn’s disease, chronic obstructive lung disease, diabetes mellitus, multiple sclerosis and insomnia are most prevalent. The metabolic changes include abdominal obesity, impaired glucose regulation and hypertension which have affected the normal population. It has been found that adipose tissue also have some immunological functions. The adipocytes release adipokines, resistin and leptin which mediates insulin resistance. Atherosclerotic plaque exhibits inflammatory infiltrates such as TNF α and interleukins (58). The cytokine levels are also associated with unstable angina and myocardial infarction, which can also be observed in psoriasis. In psoriasis, increased levels of Angiotensin Converting Enzyme (ACE), endothelin-1 and renin have been observed, thus promoting thrombotic state in the body. Most patients suffering from psoriasis get prone to depression and associate themselves with increased alcohol consumption, food intake and reduced physical activity, all aggravating the obesity and metabolic imbalance (59). Thus, if we consider the relation between psoriasis and co-morbidities the treatment plans must be adjusted so as to prevent the severe effects. Those patients which are already suffering from one or more diseases must be addressed by multidisciplinary approach before initiating a therapy for psoriasis.

**Conclusion**

Psoriasis has a large psychological impact on human health, as it is related to the appearance of the person. Although biological therapies with immune system modulators have modernized the psoriasis therapy, still proper therapy and agents need to be developed. The management of psoriasis is a problematic issue due to its continuous relapse and long duration of the disease. The utilization of initially used therapies such as arsenic and mercury derivatives has been suspended completely due to their potential side effects. Ultraviolet light therapy and Excimer lasers in combination with different oral and topical agents are widely used depending upon the severity of disease. Steroids became the drugs of choice in earlier seventies and still widely used, but possess very strong side effects. Cell growth inhibitors and antimetabolites along with biological therapies are recommended under complete medical supervision. Compiling the therapies and the molecules involved in treating psoriasis, it can be concluded that, biological therapies along with novel carrier systems providing selective targeting of molecules will be the most successful treatment in future. By understanding the mechanisms at molecular level and drug targeting based on a rationale approach will refine the psoriasis therapy. With the advancement and new approaches, wider options are being generated and these will help the patients to obtain an optimum level of treatment.

**References**

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