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Current and Evolving Strategies for the Treatment of Psoriasis: An Overview

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Abstract

An autoimmune skin condition, Psoriasis, is characterized by inflammation, vasodilatation, and hyperproliferation which results in itching, redness, silver-white dry patches on the skin. Various treatment options such as anti-inflammatory, anti-proliferative, phototherapy as well as immunosuppressants are explored through different routes such as oral (tablets and capsules), topical (creams, ointments, lotions and gels) and parenterals (intravenous, subcutaneous and intramuscular). But oral route suffered with adverse effects such as hepatotoxicity, nephrotoxicity,etc. These limitations are overcome by advancements of novel drug delivery systems (NDDS). These are liposomes, microemulsions, and solid lipid nanoparticles, etc. In this review, we have emphasized about psoriasis, its prevalence rate in India, various currently used and advanced treatment options.

Keywords*: psoriasis, skin, topical, oral, novel drug delivery system*

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1. Psoriasis - An autoimmune disease

A disease state condition in which there is an abnormal immune response to a body part. In this body immune system attacks normal body healthy cells. Different types of autoimmune diseases are psoriasis, lupus, multiple sclerosis, Type I diabetes, psoriatic arthritis and vasculitis. Amongst them, psoriasis is well known as an inflammatory condition of the skin affecting 125 million people worldwide as per International Federation of Psoriasis Association (IFPA).

Psoriasis is triggered by inflammatory mediator which is produced by T cells. It is differentiate by redness, itching and silver-scaly plaques on the skin which affects the patients both physically and psychologically. There are number of treatment options available but till date, no one is reported as safe, effective and patient compliant. This disease generally affects the people with age group of 20 to 30 years [1]. International Federation of Psoriasis Association (IFPA) annually organizes "World Psoriasis Day" on 29th of October and several societies and organizations are working towards the support of patients suffering from the stigma of this disease. Psoriasis can be categorized as mild, moderate and severe as per the affected body surface area (BSA) [2]. Several environmental factors act as triggering agent in the initiation of psoriasis alter the skin barrier.

2. Types of Psoriasis

Different types of psoriasis have different signs and symptoms but red, scaling plaques of itchy, elevated skin is common in all. The most common type is plaque psoriasis. Various types of psoriasis are discussed below [1].

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2.1. Plaque psoriasis is the thickened red patches with silvery-white scale formation on the skin. These patches are commonly found in knees, lower back and scalp. Patches width generally ranges from 1-10 cm. Depending upon severity of disease size of patches varies.

2.2. Guttate psoriasis seems on skin as small red spots and ranked as second most common type, affects about 10 percent of the population. Size of spots is small and they are drop-shaped. They are oftenly found in torso, limbs, face and scalp and with time these spots can turn into plaque psoriasis.

2.3. Flexural or inverse psoriasis mainly affects the skin folding of the breasts or armpits. Patches are red and often shiny and smooth. This type of psoriasis can be confounded as bacterial or fungal infections.

2.4. Pustular psoriasis is severe form of psoriasis spreads as white pustules surrounded by red skin. Mainly occurred on hands and feet and affects most of the skin's surface. Scaling is formed by joining the pustules.

2.5. Psoriatic arthritis (PsA) is painful condition affecting 10 to 30 percent of patient. Five types of PsA are there, namely-Asymmetric oligoarticular, Symmetric polyarthritis, Distal interphalangeal predominant, Spondylitis and Arthritis mutilans. Each type has different type of symptoms. It can affect manly joints.

2.6. Scalp psoriasis characterized by silver-white scaly plaques of thickened skin. It can extend beyond forehead and can also reach to ears.

2.7. Erythrodermic psoriasis or exfoliative psoriasis seems as severe burns and may cover large portion of the body. It is a chronic condition which is widespread as red and scaly skin condition.

3. Pathogenesis - Alteration in skin barrier due to environmental trigger factors and genetic defects contribute to progression of disease through production of self-DNA, leading to formation of plasmacytoid Dendritic Cells (DCs) and mature Dendritic Cells. Mature DCs produces multiple cytokines such as Th17, Th1 andTh22 cells. Both cytokines and Th17, Th1 cells leads to production of CCL20, a chemoattractant by keratinocytes, leading to accumulation of these cells in the area of psoriatic lesion. On stimulation of DCs and proliferating keratinocytes by Th17, IL-20 is produced which promotes keratinocyte hyper-proliferation and causes inflammation. Released IL-6, IL-1β and TNF-α leads to enhanced DC activation and expanded the local inflammation [3]

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4. Psoriasis - Epidemiological pattern In India

Descriptive study was performed on 400 patients, visited the dermatology department at Chengalpattu Medical College for a period of 3 months from January 2019 to March 2019. Study concluded that as per: a) sex ratio - cases reported in males were twice to that in females, b) age of onset – more in females as compared to males from less than 15 years to 50 years, c) clinical pattern – Out of 400 patients, 212 patients were diagnosed with plaque psoriasis, i.e. more than 50%, around 127 patients were diagnosed with palmoplantar psoriasis, and 37 patients with scalp psoriasis. While remaining patient are suffered with other types such as genital, erythrodermic, flexural, guttate, nail, and pustular psoriasis which constituted around 6% of total cases.

5. Treatment Options

5.1. Topical - Medicaments are applied to the skin and rubbed for getting local relief without having any systemic side effects as in case of medicines taken orally. This treatment includes the following [4-7]:

1. Calcitriol and Calcipotriene containing topical ointment- These are effective when used with topical corticosteroid cream.
2. Corticosteroids - These are used as first-line therapy for psoriasis covering small areas of the skin. Steroids are available in different strengths and are usually applied once or twice daily. These are available in the form of creams, gels, sprays, foams, and ointments. It was found that corticosteroids have the lowest risk rate of causing adverse events and that usually used in concentration range from 3.2% to 23%. However, its long term usage leads to skin atrophy and thinning.
3. Coal-tar shampoos and ointments – Their mechanism is to slow down the rapid growth of skin cells and their symptoms and can be prescribed only under the supervision of practitioner as their use can cause folliculitis, skin thinning and skin cancer.
4. Moisturizers- They contains salicylic acid, lactic acid, urea, and glycolic acid and they work by reducing the thickened scales that prevent movement of topical medications into the deeper layers of the skin. They are applied one to three times a day on the body.
5. Anthralin- Currently it is used in combinatorial treatment with ultraviolet B phototherapy in current practice. Problems associated with it are- local skin irritation and staining of skin. Short-contact treatment regimen has been made to get rid of above-mentioned problems,

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6. Vitamin D analogues- When applied topically they inhibit keratinocyte growth as well as it also decreases inflammation in lesions as it regulates the immunity,

5.2. Phototherapy- The different mechanisms involved in the treatment of psoriasis using photo therapy are alteration in cytokine profile, promoting apoptosis and immunosuppression [8,9**].** These are as follows:

1. PUVA (Psoralen combined treatment with ultraviolet A light) is one of the most effective treatment but of less importance today as the risk of developing skin cancer is high, even after withdrawal of the therapy.
2. Narrow-band UVB therapy is almost as effective as PUVA and has less chances of causing cancer
3. Ultraviolet B light (UVB) light is used in treatment for mild form of psoriasis

5.3. Oral - One of the most common route of systemic treatment and mostly prescribed for severe psoriasis. Several drugs used orally are:

1. Acitretin- It is an oral retinoid (a form of vitamin A used for treatment of moderate to severe psoriasis. It causes serious side effects like depression, liver damage, chapped skin and dry mouth.
2. Methotrexate- It inhibits folate biosynthesis by interfering the synthesis of deoxyribonucleic acid. It is used in moderate to severe form of psoriasis and also in psoriatic arthritis because of its anti-inflammatory and cytostatic action. It is often dubbed as the-gold standard for psoriasis treatment. The major side effect is hepatotoxicity and other common side effects seen are nausea, vomiting, diarrhea, and fatigue.
3. Cyclosporine: It works by inhibiting calcineurin. It is used for treatment of moderate to severe form of psoriasis and also used in case of psoriatic arthritis. Complete remission was seen in 80% - 90% of patients in a 1-year open and randomized study with 400 patients within 12- 16 weeks, [10]. It shows rapid onset of action. The common adverse effects seen are elevated triglyceride levels, nephrotoxicity, hyperkalemia and hypertension. It can also cause skin cancers. Its efficacy has been shown by various randomized studies in treatment of plaque psoriasis. Moreover, it shows dosage-dependent therapeutic effect, when the drug is given for 10–16 weeks and dose ranges from 1.25 to 5 mg/kg/day [11].

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4. Apremilast- It inhibits PDE4, ultimately leading to increased amount of cyclic adenosine monophosphate (cAMP) causing decreased production of inflammatory cytokines such as IL-23 and increased formation of anti-inflammatory mediators [12].
5. Tofacitinib- An oral immune response regulator which inhibits Janus kinase (JAK) mainly targeting JAK1 and JAK3. It is used treatment of chronic plaque psoriasis [13].

5.4. Biologics-Currently available biologics for treatment of psoriasis in India are- etanercept, infliximab, secukinumab and itolizumab. Biosimilars are also available for management of psoriasis. Patients are given biologics only when the eligibility criteria are fulfilled by the patient but these therapies shows toxicities issues too (shown in Table 1).

5.4.1. Tumour Necrosis Factor alpha (TNF-α) blockers- Soluble TNF cytokine (sTNF) and transmembrane TNF (tmTNF) causes inflammation by activation of NF-kB after binding to TNF receptor 1 and TNF receptor 2. Currently used TNF blockers are Infliximab, adalimumab. Infliximab is used for treatment of severe psoriasis and moderate to severe form of psoriatic arthritis. Therapy is started by giving 5 mg/kg of dose at 0th, 2nd, and 6th week.

5.4.2. Anti-CD6 antibody - Itolizumab is recently approved IgG1 monoclonal antibody which binds to CD6 thereby down-regulating activation of T cell, reducing synthesis of pro-inflammatory cytokines, and also reduces infiltration of T cell at site of inflammation, [14].

5.4.3. Anti-Interleukin (IL) 17Aantibody - Secukinumab is human IgG1K antibody that selectively targets and neutralizes IL-17A, thus causing recruitment of- Th17 cells, dendritic cells, neutrophils. The drug has shown its efficacy in treatment of moderate to severe form of plaque psoriasis in phase 3 trial, [15].

Table 1- Indications and reported toxicities of biologicals

S. No.	Biological	Indications	Toxicity
1.	Itolizumab	Moderate and severe form of plaque psoriais	Infections
2.	Secukinumab	Moderate and severe form of plaque psoriasis, Psoriatic arthritis	Candidal infection, Inflammatory bowel disease
3.	Etarnecept	Moderate and severe form of- plaque psoriasis and Psoriatic arthritis	Congestive Heart Failure

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6. Recent advancements – Novel Drug Delivery Systems in Psoriasis

Transdermal delivery of drugs faces many challenges, such as first pass metabolic activity of skin, skin irritation, skin damage due to drug toxicities and differences in percutaneous absorption because of site, age, etc. Novel drug delivery systems are more beneficial as compared to conventional dosage forms. Advancements in Novel drug delivery systems are shown in table-2.

6.1. Nanocarriers - Nanocarriers of Solid in oil (S/O) are used as the vehicles for the transdermal delivery of methotrexate (MTX) which is used to treat severe and moderate psoriasis. Systemic side effects include hepatic toxicity, loss of vision, hair loss. These side effects can be reduced with help of topical delivery of drugs, capable of targeting the affected cells. These nanocarriers increase penetration of MTX through SC. Liposomal delivery of MTX reduces sub-cutaneous offered drug resistance because liposomal lipophilic conjugates increase diffusion of MTX through plasma membrane [16].

6.2. Hydrogels - These are the polymeric gels with high molecular weight. They enhance MTX topical delivery effectiveness by iontophoretic mechanism [17].

6.3. Liposome - These are the widely used vehicles for topical delivery systems. Surfactants are present inside the liposome works by breaking the lipid bilayer helping the drug to permeate easily through skin. They have been used to reduce the solubility issues of temoporfin. More concentration of temoporfin can be found from surface modified liposomes [18]. Moreover, PEGylated liposomes also have better effect in delivering drugs to epidermis.

Dithranol is often used in topical therapy of psoriasis but, when used as ointment it shows problems like irritation and staining of clothes. Skin penetration was improved when dithranol was used with liposomal systems, [19]. It was found that liposomal and niosomal systems entrapped with dithranol show better effect as compared to conventional dosage form, [20]. When dithranol is given using liposomal systems there are no problems in terms of irritation and staining of clothes [21].

Another study reports that deformable liposomal formulations of MTX are superior to aqueous solution and normal liposomal formulation of MTX invitro. Moreover, ethosomes also have shown better skin permeation characteristics, [22]. MTX formulated in form of oil in water (o/w)

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micro-emulsions system had higher permeation flux than compared to permeation flux corresponding solutions in mice skin, [23]

6.4. Nanoemulsions - There are many advantages of using these as it can deliver poorly water soluble drugs into the depth of skin layer. Particle size ranges from 10nm to 200 nm. Absorption of drug is also increased and also the release of the drug can be controlled.

6.5. Pro-dispersion liposphere - Formulations composed of dispersing agents, amphiphilic solvents and solid fat for delivery of lipophilic drug cyclosporin by using pro-dispersion lipospheres. A solution containing cyclosporin, ethyl lactate, surfactants, lipids were mixed and on addition of this solution to aqueous media, dispersion system was formed. Pro dispersion liposphere system not only enhanced bioavailability of water insoluble drugs but also improved the stability of the drug [24]

6.6. Solid lipid nanoparticles

Tretinoin is used for skin diseases like - acne, photoaging and psoriasis. It can cause skin irritation. Such drawback can be reduced by encapsulation of drugs. It increases the drug stability. Tretinoin incorporation into solid-lipid nanoparticles provides sustained release, stability. Chitosan solid-lipid nanoparticles have been used as they have high compatibility with tretinoin and possess many advantages such as - bio adhesion, wound healing and anti-bacterial activity. Tretinoin effects combined with the chitosan anti-bacterial activity resulted in efficient treatment for psoriasis [25].

Table 2- Advancement in topical therapy using novel drug delivery systems

S. No.	Drugs	Delivery System	Advantages
1.	Methotrexate	Solid lipid nanoparticles	Improved Therapeutic index
2.	1,25-dihydroxyvitamin D	Liposomes	Improved efficacy
3.	Dyphylline	Liposomes	Enhanced permeation
4.	8-methoxypsoralen	Microemulsions	Enhanced skin accumulation
5.	Triptolide	Microemulsions	Enhanced permeation
6.	Tamoxifen	Multilamellar liposomes	Enhanced skin permeation

7. Conclusion

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Psoriasis is an auto-immune inflammatory disease, which is chronic in nature. It is characterized by scaly plaques with thickening and proliferation of cells on the epidermal skin layers. The main trigger factor is the inflammatory mediator produced by T cells. The disease can be mild within which there is involvement of the small areas of the skin. In severe cases, whole body is affected having thick plaques. For treatment, different therapy regimens are available having their own advantages and disadvantages. To get effective drug delivery, novel drug delivery systems are explored. Recent advancements and role of nanotechnology overcome the challenges and side effects of conventional treatment and provide optimum efficacy, targeted delivery, improved drug permeation, reduction in adverse effects and recurrence of psoriasis condition, which can provide a new platform in the topical therapy of psoriasis.

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