

EXISTING AND NOVEL THERAPIES FOR PSORIASISCH. NAGA NAVYA¹, GAURAV K JAIN², VIKAS JAIN^{1*}¹Department of Pharmaceutics, J.S.S College of Pharmacy, Mysore, Karnataka, India. ²Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi India. *Email: vikasjain@jssuni.edu.in

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ABSTRACT

Psoriasis is adjudged as prototypic papulosquamous skin condition attributed by the erythematous papules (or) plaques. It occurs at any age but commonly seen in age groups of 20–30 and 50–60 years. Psoriasis affects around 2% of the world population. Psoriasis has a broad spectrum of skin indications occurring in different forms with common characteristics. It is clinically classified as non-pustular and pustular psoriasis. Existing therapies include topical therapy, systematic therapy, and phototherapy. Biological drugs and novel immunological factors have been identified as alternative therapy to conventional therapies. These biological drugs show more efficacies with fewer side effects in long-term application.

Keywords: Psoriasis, Biological therapy, Anticytokine therapy, Phototherapy.

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INTRODUCTION

Psoriasis is characterized by papulosquamous skin condition with erythematous papules (or) plaques. Dysregulation of the immune system leads to red, scaly, flaky, chronic inflammatory, and itchy patches with increased keratinocytes proliferation [1]. Sometimes, the body's immune system cannot differentiate between the foreign particle and its own. During the process of defending itself against infection, it may lead to excessive skin cell proliferation. Psoriatic arthritis refers to psoriasis that affects the joints. The severity of psoriasis varies among individuals of different age groups. Psoriasis impacts patient's psychological stress due to its appearance. This stress may trigger psoriasis even more which might worsen the condition at times. Psoriasis is prevalent in 2% population around the world, mainly seen in the age groups of 20–30 and 50–60 years. Plaque psoriasis is prevalent among 80% of individuals, of which around 33% suffers from mild diseases and remaining from moderate-to-severe conditions [1,2]

TYPES OF PSORIASIS

Psoriasis is classified into a broad spectrum of skin indications. It is generally divided into pustular and non-pustular forms. A person can represent different forms of psoriasis at the same time. It can affect any part of the body. However, all forms show common characteristics like erythema with thickened scales, and the size of lesions varies from a pinhead to 20-cm diameter. These lesions may appear oval, polycyclic, or round in shape [Table 1] [3,4].

Psoriasis vulgaris

About 90% of cases are noticed as psoriasis vulgaris in clinical form. It appears as erythematous plaques which are covered by silver scales. Lesions distribute symmetrically and frequently occur on the knees, scalps, sacral region, and elbow. If psoriatic plaques surface is scraped with a blunt scalpel, flakes fall off as layers and it exhibits a phenomenon called as "wax spot phenomenon." Further scrapping discloses a wet layer attached to the lesion, and this is the last layer of dermal papillae which is referred as "last membrane phenomenon." If it is scraped further, an erythematous background and bleeding foci which look like red pinpoint referred as "Woronoff ring" are observed. There is no clarified pathogenesis for this ring. However, it may be due to a reduced level of prostaglandins in healing lesions [5-8].

Guttate psoriasis

It is mostly seen in children and young adults. The lesions structurally look like small droplets and rarely convert into squamous psoriatic papules. It usually manifests after a streptococcal infection. It is generally linked with HLA-Cw6 gene. These types of psoriasis occur on the trunk, proximal part of extremities, scalp, and face. They usually revert within 3–4 months, but in rare cases, it develops into plaques [9].

Erythrodermic psoriasis

Nearly 80% of the lesions that affect body surface are categorized as a generalized form of psoriasis, plaques, and papules which lose their attributes. Desquamation is not so definite, but it causes protein loss as well as some systematic problem such as edema of lower extremities, and cardiac, hepatic, and renal failure. Damage of skin barrier results in systematic reactions, which in turn leads to the development of psoriasis vulgaris or erythrodermic psoriasis [10].

Palmoplantar psoriasis

In general, palmoplantar psoriasis occurs on palms, hands, and soles of the feet. It affects more on thenar regions than the hypothenar region. Usually, erythema does not appear, but incase if it exists, then it appears as pinkish yellow lesions. Scales are the main lesions, and thick flakes may provide an appearance of keratoderma [11].

Inverse psoriasis

Inverse psoriasis or flexural psoriasis is localized in skin folds. Scaly lesions do not form because of friction and moisture produced between the skin folds. This form of psoriasis is diagnosed with fissured plaques. It is commonly observed in obese individuals with a tendency to develop a seborrheic lesion. This type of psoriasis refuses to accept classical therapy [10].

Generalized pustular psoriasis

It is the rare form of psoriasis with pustules, usually observed in young individuals. It either develops independently or seen as a complication of psoriasis vulgaris. In this form, leukocytosis, lymphopenia, and nitrogen balance will be increased. Within few days, pustules get dried, and new pustules arise within no time. Peripustular erythema has behavior to spread which leads to erythrodermia. The disseminated region should be promptly treated; otherwise, acute phase may cause to the fatal course [10-12].

Table 1: Clinical classification of psoriasis

Non-pustular psoriasis	Pustular psoriasis
Psoriasis vulgaris	Generalized pustular psoriasis
Guttate psoriasis	Impetigo herpeticiformis
Erythrodermic psoriasis	Localized pustular psoriasis
Palmoplantar psoriasis	
Inverse psoriasis	

Impetigo herpeticiform

This type of psoriasis is rarely seen, referred to as generalized pustular psoriasis of pregnancy. It contains erythematous lesions with pustules. It involves mucous membrane and onycholysis secondary to subungual pustules. The lesions cause itching or burning sensation with a foul odor. It also shows some additional symptoms such as fever, shivering, nausea, and vomiting. It is related with hypocalcemia. Commonly, it occurs during subsequent pregnancies.

Localized pustular psoriasis

It is subdivided into two forms as Barber's-Pustular psoriasis and Acrodermatitis continua of hallopeau.

Barber's-pustular

In general, it is found in women with a family history of palmoplantar pustulosis. It is chronic, with 2–4 mm sized pustules which are located on the palmoplantar region. Its etiology is merely known. This disease is triggered by smoking, tonsillitis, humidity and high temperature.

Acrodermatitis continua of hallopeau

It comes under skin disorder which contains sterile pustular eruption located on fingers and toes. It involves loss of nails and distal phalanges in severe conditions. Pustules join together to form small, polycyclic, purulent, fluid-filled vesicles [13].

PSORIATIC ARTHRITIS (PSA)

Its prevalence varies between 5.4 and 7% among patients. Pustular psoriasis prevalence ratio rises to 30–40% during psoriatic arthritis condition. During the onset of the second or third decade of the life of an individual, uncomplicated psoriasis begins and prevalence of psoriatic arthritis increases in the third decade. Psoriatic arthritis divided into five subgroups by "Moll and Wright" based on clinical form as classical PsA, asymmetric oligoarticular arthritis, symmetric polyarticular arthritis, arthritis mutilans, and spondylitic form [14,15].

Classical PsA is observed in mere 10% of individuals. It affects distal interphalangeal joints of the hands and feet. Asymmetric oligoarticular arthritis appears in 11% of cases, and it affects major joints such as knee joints and proximal and distal interphalangeal joints. It also shows the symmetrical effect on the metacarpophalangeal and metatarsophalangeal joints. Symmetric polyarticular form looks similar to rheumatoid arthritis, while arthritis mutilans is distinguished by progressive osteolysis of phalangeal and metacarpal bones. In general, it appears on the hands, but sometimes, its presence can be observed on the feet with similar involvement. Spondylitic form is linked with peripheral arthritis, where the involvement of spondylitic joints and symmetric or asymmetric sacroiliac joint is seen.

PATHOPHYSIOLOGY

Cathelicidin belongs to AMP family in the skin which shows various immune regulations. Cathelicidin (LL-37 form) and DNA-complex together activates plasmacytoid dendritic cell. During psoriatic conditions, human cathelicidin peptide, especially active form of LL-37, is overproduced and aggregates with self-DNA, which leads to the formation of stable complexes. These stable complexes are recognized by plasmacytoid dendritic cell through TLR9 in the dermis. Thus, activated plasmacytoid dendritic cell releases interferon alpha and beta (INF- α and INF- β) which triggers local maturation of myeloid dendritic cell. These myeloid dendritic cells activate T-cells which are

differentiated into T-helper (th1 and th17), which leads to autoreactive inflammation in psoriasis [16].

TOPICAL PSORIASIS THERAPY**Corticosteroids**

In topical psoriasis treatment, corticosteroid remains a mainstay. Its mechanism is not precisely known. It acts as an anti-inflammatory, immunosuppressive, and anti-proliferative agent by showing influence on gene transcription. Due to its occlusive property, ointments are more effective. Its efficacy depends on skin type and plaque thickness [17,18]. Flucinonide (0.005% w/v as solution/foam), clobetasol (as 0.005% w/v shampoo/spray), hydrocortisone (1% w/v), and betamethasone (0.005% w/v) are most commonly employed active agents under this category.

Vitamin D analogs

In the treatment of psoriasis, Vitamin D analogs such as calcitriol, calcipotriol, and tacalcitol are involved. In some patients, monotherapy of Vitamin D analogs is effective, whereas the combination therapy (corticosteroid and Vitamin D analog) shows better efficacy. In the United States, calcipotriene was used as topical Vitamin D analog until 2009, in the form of a cream, ointment, foam, or solution. In Europe, the topical Calcitriol ointment is being used, as it shows less irritation when compared with calcipotriene [19,20].

Calcipotriene

Calcipotriene is also referred as calcipotriol and it is accepted therapy for psoriasis. Its mechanism is not precisely known, but it mainly shows its efficacy on hyperproliferation of keratinocytes, and it also shows efficacy on immune modulation, but it does not show outstanding results in psoriasis therapy. Combination therapy (corticosteroid and calcipotriene) depicts a rise in clinical response. Combination of calcipotriene with betamethasone propionate (0.064%) shows more efficacy than monotherapy. Corticosteroid and calcipotriene are generally applied twice a day, individually however, a combination of these two drugs is administered only once in a day. As calcipotriene becomes inactive in the presence of acidic moieties and some corticosteroid are acidic in nature, owing to which the data related to controlled clinical trial are very sparse to claim the rationale behind the usage of combination therapy. However, a combination therapy had reasonable approaches when patients used both calcipotriene and corticosteroid at different times, once daily. Adverse effects are generally minimal a part of skin irritation [21,22].

Calcitriol

Calcitriol mechanism resembles calcipotriene, which shows efficacy on hyperproliferation of keratinocytes and inhibits inflammatory mediator. In a controlled study, perilesional erythema, perilesional edema, and burning sensation were reduced in calcitriol-treated areas [23,24].

Tar

The popularity of psoriasis therapy with tar is now reduced because of the availability of some new therapies. Its mechanism is not clearly known, but it acts as an antiproliferative agent. Tar can also be used with topical corticosteroid. However, it is not commercially available. Tar can be used without a prescription and is available in the form of shampoo, cream, lotion, oils, ointments, solution, and foam. In general, 2–3% of tar with 0.1% of triamcinolone cream can be applied twice per day to treat plaques. 1% of tar in fatty acid based lotion shows more efficacy than 5% conventional tar, and this 1% tar lotion resembles calcipotriene, efficacy wise. Tar produces unpleasant odor and it also tends to be messy [25,26].

Tazarotene

Tazarotene is safe and effective topical retinoid used in psoriasis therapy. 0.1% cream is more effective than 0.05%, but it causes some local adverse effects. As absorption of Tazarotene is minimal, systemic toxicity is unlikely to even in long-term therapy. Application

of tazarotene for 20 min followed by washing causes less irritation compared with traditional use [27,28].

Calcineurin inhibitor

0.1% of topical tacrolimus and 1% pimecrolimus have good efficacy in treating facial and intertriginous psoriasis, and it is well tolerated too. Application of 0.1% pimecrolimus twice a day shows almost clearance of lesion. However, when compared to corticosteroids, it is less efficacious [29-31].

Anthralin

Since the early 20th century, topical anthralin is used for psoriasis therapy and it has good efficacy. Its mechanism of action is not clearly known, but it has an anti-inflammatory effect and antiproliferative effect. Adverse effects of anthralin are skin irritation and red-brown stains which are temporary. The therapy starts with low concentration like 0.1% or 0.25% for 10–20 min application per day for minimal skin irritation and slowly increased until it reaches to contact time of 1 h. Then, slowly, the concentration of anthralin is increased on the basis of lesion response and tolerance of the patient. In the United States, 1% or 2% cream and shampoo of anthralin is commercially available. Application time is usually 5–10 min/day, which is gradually increased up to 20–30 min depending on the tolerance of patient. The normal skin should not get in contact with anthralin as it causes skin irritation. We can protect unaffected skin by identifying plaques or by applying petroleum or zinc oxide to the unaffected skin before anthralin application [32-34].

PHOTOTHERAPY

Ultraviolet (UV) light

Psoriasis can be controlled using ultraviolet light. It acts as antiproliferative and anti-inflammatory agent. For this therapy, taking advice from a trained dermatologist is important. According to AAoD, UV-B radiation (290–320 nm) can be administered as monotherapy or in combination with tar. The inducing dose of UVB for patients should be weekly 3 times. Once it achieves remission, maintain the regimen which is recommended to prolong the remission [35]. Narrowband UV-B having a range of 311 nm is an alternative standard for psoriasis therapy apart from broadband 290 to 320 nm. Narrowband UV-B dose shows more efficacy than broad band UV-B dose to clear plaque psoriasis and apoptosis [36,37].

UV-A radiation or photochemotherapy (PUVA) warrants strict medical supervision. As compared to UV-B, UV-A can go deeper into dermis without causing any skin burn. This therapy involves either oral or topical (bath) administration of psoralen. If a patient undergoes oral therapy, then photosensitizing drug, 8-methoxy-psoralen is injected in patient followed with UVA exposure for 2 h. This process happens thrice a week until dose increment gets remission. Later, recommended dose should be maintained either twice or once weekly. If a patient undergoes bath PUVA, then affected area of a patient is soaked for 15–30 min in psoralen mixed with water before UVA exposure [38].

Photoprotection such as sunscreen, hat, and sun protective goggles is used pre- and post-treatment to avoid skin and ophthalmic injuries due to the exposure to UV rays. As emollients inhibit UV penetration into the skin, it should not be applied to the skin before treatment.

Home phototherapy

Home phototherapy (or) home UV-B is alternative method for office-based phototherapy. This method should be followed only when the clinician suggest it to follow by your own. Excessive use of this device should not be practiced, and it should not exceed the number of treatment that is prescribed by clinician. To avoid overexposure, electronic control is equipped with home phototherapy devices, which allows only prescribed numbers of therapies [39].

Excimer laser

Excimer laser at a range of 308 nm produces high energy. This is another method with a higher dose of UV-B involvement in the treatment of only affected skin. It gives faster results when compared

with conventional phototherapy. Application of this therapy shows erythema and blistering. However, it can be tolerated easily and it has not been considered as major side effect by patients. UV-induced hyperpigmentation (tanning) is caused by excimer laser, but it can be controlled after termination of therapy [40,41].

Saltwater bath

It is proved that natural sunlight with sea water combination can also treat psoriasis. Hence, salt water bath with artificial ultraviolet exposure is being used for treating psoriasis. Additional factual studies are needed to establish the potential of the said therapy for full-fledged application [42].

SYSTEMIC THERAPY

Methotrexate

Since 50 years, folic acid agonist methotrexate is used to treat psoriasis and it also shows efficacy for psoriasis arthritis and psoriatic nail disease. Initially, its mechanism of action was centered on antiproliferation, but later, it was considered as immunosuppressive agent, evidenced by the latest studies. It shows efficacy on activated T-cell which helps in the treatment of psoriasis. Methotrexate shows less efficacy compared to adalimumab. Methotrexate is recommended to be administered once weekly through oral, intravenous, intramuscular, or subcutaneous routes, and the range of administration is 7.5–25 mg/week [43-45].

Retinoids

Severe psoriasis can be treated with systemic retinoids. It also treats pustular and erythrodermic form. HIV-associated psoriasis patients also get treated with systemic retinoids. Acitretin is the retinoid used to treat psoriasis within the dose range of 25–50 mg/day. Good results are seen when acitretin is used in combination with phototherapy. Adverse effect associated with retinoids therapy is cheilitis and alopecia [46-49].

Calcineurin inhibitor

Severe instances of psoriasis are treated with cyclosporine, a calcineurin inhibitor. It acts as T-cell suppressor and administered in the dose range of 3–5 mg/day, orally. Within 4 weeks of treatment, massive improvements in patient's condition can be seen. However, long-term use of cyclosporine results in renal toxicity and hypertension [50-52].

Apremilast

Moderate-to-severe plaques are treated with apremilast. It acts as *phosphodiesterase-4* inhibitor which helps in decreasing the production of multiple cytokines which cause psoriasis pathogenesis. The therapeutic dose of apremilast is 30 mg twice per day; however, it is considered to be less efficacious when compared with cyclosporine, ustekinumab, and anti-tumor necrosis factor (TNF) therapies [53-57].

NOVEL THERAPIES

Anti-TNF therapy

TNF- α (a cytokine) induces inflammation in psoriasis by involving multiple pathways. It raises adhesion molecules on the vascular endothelial cell that facilitates inflammatory cells into lesion. It also stimulates keratinocyte of other pro-inflammatory mediators and activates dendritic cell and macrophages. Recent studies suggested that TNF- α inhibitors play a major role in the treatment of psoriasis [58].

TNF- α gets neutralized by infliximab. As it binds to TNF- α and permanently gets it deactivated, it helps in the inhibition of inflammatory cytokine production and relieves from the symptoms of psoriasis [59,60]. Adalimumab and certolizumab pegol are absolutely humanized monoclonal antibodies explored for the management of psoriasis, currently available in the market, administered every 2 weeks. They do exhibit the same mode of action as that of infliximab.

Synthetic receptors such as etanercept have higher empathy for TNF- α as compared to natural receptors. This high binding affinity results in neutralization of TNF- α -mediated psoriatic inflammation. It can be administered twice a week [61-63].

Other anticytokine therapy

Pro-inflammatory cytokines are a mediator for various biological processes, and it gets stimulated in the body by increasing the level of cytokines that lead to many pathologies, autoimmunity, and cancer. These anticytokines block the antibodies and neutralize the cytokines [64].

Ustekinumab

Dendritic cells produce two interleukin subunits, interleukin (IL)-23 and IL-12, which play a role in pathology. This Ustekinumab binds to IL-23 and IL-12 which inhibits signal transduction pathways and shows differences in T-cell as Th1 and Th17. Hence, IL-23 and IL-12 blockage leads to reducing the number of Th1 and Th17 in the blood [65].

Apilimod

In myeloid leukocytes synthesis, IL-12 and IL-23 get suppressed by Apilimod, which is developed from triazine derivative. Recent studies proved that apilimod not only inhibits IL-12 and IL-23 but also multidownstream cytokines in the affected skin and increased synthesis of IL-10, an anti-inflammatory cytokine [66,67].

Brodalumab

IL-17 plays a major role in the survival of the psoriatic disease. Brodalumab acts as human anti-IL-17 receptor which suppresses the efficacy of IL-17A, IL-17F, and IL-17A/F [68].

Ixekizumab

Ixekizumab is a novel human monoclonal antibody. IgG4 acts as anti-IL17 by blocking cytokines, beta-defensins, and antimicrobial peptides production in keratinocytes. It also suppresses chemokines which are responsible for skin lesions. Moderate-to-severe plaques psoriasis can be treated by Ixekizumab [69].

Alefacept

LFA-3, which is expressed on antigen presenting cell, binds to CD2 molecule and results in the production of mature T-cell and natural killer cells. Hence, this LFA-3 with CD2 molecule will produce a signal that results to the activation of naïve T-cell in effector cell. Alefacept blocks the interaction between CD2 molecule and LFA-3 and, hence, prevents T-cell activation and proliferation [70,71].

Small molecule inhibitor

Small molecules inhibitors serve as better alternatives to treat psoriatic conditions which remain untreated with conventional therapies. These agents assist in inhibiting signaling pathways that help in eliciting inflammatory cytokines [72]. Different categories of therapeutic agents are being discussed here.

Phosphodiesterase-4 inhibitor

T-cell secretes inflammatory cytokines such as IFN- γ , TNF- α , and IL-12 from monocytes in blood. Inhibition of phosphodiesterase helps in suppressing T-cell secretion [53,73-75].

Protein kinase inhibitor

Protein kinase C inhibition helps to inhibit classical and novel protein kinase C which regulates immune signaling cascade and INF- γ and IL-17 production [75,76].

Mitogen-activated protein kinase inhibitor

Different inflammatory diseases have been chronicled the importance of nitrogen-activated protein kinase. It shows involvement in cell proliferation, inflammation, and differentiation. p38-MAPK is over expressed in psoriatic lesions and BMS582949 is identified as a novel selective p38-MAPK inhibitor [77,78].

Janus kinase inhibitor

Several cytokines receptors are connected with Janus kinase which belongs to cell-signaling molecules. Janus kinase activates STAT pathway which controls the expression of a nuclear target in gene and induces pro-inflammatory gene. JAK3 shows involvement in IL-2, IL-6, IL-7, IL-15, and IL-21 signaling. Tofacitinib inhibits the JAK1 and JAK3. ASP015K4 and VX-509 inhibit JAK3, and INCB28050 inhibits JAK 1 and JAK2 [79,80].

Nerve growth factor inhibitor

Large quantities of neuropeptides are released by sensory nerve fiber due to stress. Research also proved the link between emotional stress and peripheral nervous system, resulting in the onset of psoriasis lesion. T-cell activation, keratinocytes proliferation, angiogenesis, and cutaneous nerve proliferation have been activated by nerve growth factors which are present in psoriatic lesional and non-lesional plaques. K252a and CT327 act as NGF inhibitors and available as topical therapy.

OTHER THERAPIES**Insulin**

In dermis, IL-1 β is present in a large amount which activates P38-MAPK (mitogen-activated protein kinase). This kinase acts on insulin receptor and induces the insulin resistance in the keratinocytes, which in turn alters keratinocytes proliferation and differentiation and subsequent alleviation of symptoms related to psoriasis.

Magnetic therapy

The use of magnetic therapy with low frequency for psoriasis therapy helps for the treatment of both skin and joint manifestation. Magnetic therapy acts as anti-inflammatory for healing, soothing, reducing itch, immunostimulator, and detoxification effects. When both active periods of skin lesion and remission phase are present, this magnetic therapy is used. The affected area is attached with applicator, beneficial to liver and stomach therapy by supporting liver detoxification, metabolic function, and absorption process and adjusting the digestion. Depending on the development and course of disease, application of therapy will be given repeatedly (or) throughout sufferer lifetime.

CONCLUSION

Psoriasis is persistent, familial, non-communicable skin disease, with no precise cure. A constellation of therapy is available which can control the disease of psoriasis among people. Along with existing therapies, the novel therapies such as anticytokines, small molecule inhibitor, NGF inhibitor, and corticosteroids [81] and other therapies became more prevalent in recent years for the treatment of psoriasis. Although various therapies and drugs are present in the market, still no drugs can permanently cure psoriasis and few of them elicit severe adverse effects. Biological drugs and novel immunological factors act as alternatives to conventional therapies which give a better understanding for functional and immunological pathways of treating psoriasis. These biological drugs show more efficacies with fewer side effects even in long-term usage. Despite their huge cost, it really offers a better alternate for improving the quality of life for patients. Novel drug delivery systems are also found to be effective for the treatment of psoriasis [82].

CONFLICTS OF INTEREST

All authors have none to declare.

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