

**A REVIEW ON TOPICAL THERAPEUTICS IN PSORIASIS****Satyapal Singh***

Research Scholar, Department of Kayachikitsa, faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.

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Correspondence for*Author****Satyapal Singh**

Research Scholar,
Department of
Kayachikitsa, faculty of
Ayurveda, Institute of
Medical Sciences, Banaras
Hindu University, Varanasi,
Uttar Pradesh, India.

ABSTRACT

Psoriasis is now considered a multifactorial disorder that has several factors like genetic predisposition, environmental, immunologically mediated inflammation and several modifying factors including obesity, trauma, infection and a possible deficiency of the active forms of vitamin D3. Usually it runs a chronic course and requires timely and appropriate medical care. A wide range of treatment options are available, however, adverse effects and success vary from patient to patient. Topical therapy remains a key component for the management

of most of the patients with psoriasis. Mild disease is typically managed with topical therapy alone and moderate to severe form is usually treated with phototherapy, conventional systemic therapies or biological agents. However, use of topical therapy in moderate to severe disease may be helpful and can potentially reduce the amount of phototherapy or systemic agent required to achieve satisfactory disease control. Although phototherapy, traditional systemic agents and biological agents are available for the treatment of psoriasis, however, topical therapies continue to serve as the fundamental basis. Understanding the mechanism of action of these drugs is necessary for better management and proper application in situations where clinical challenges appear.

KEYWORDS: Psoriasis, topical medication, emollients, topical steroids.

INTRODUCTION

First line treatment usually started with topical therapies, such as dithranol, topical corticosteroids, vitamin D analogues, and tar preparations, etc. These can be prescribed in

primary care. Second line therapy usually includes phototherapies including ultraviolet B-light [UVB] and psoralen plus UVA light [PUVA]) and systemic non-biological agents such as ciclosporin, methotrexate and acitretin. These are usually prescribed by specialist dermatologists. Third-line therapy includes the use of systemic biologicals such as adalimumab, etanercept, infliximab and ustekinumab. These should be prescribed by specialist dermatologists in secondary or tertiary care settings. Best supportive treatment (care) may include a range (or combination) of the above therapies. The treatments recommended by specialists, principally in tertiary care may change depending upon clinical condition or course of the disease.^[1]

The aim of topical therapy is to minimize the extent and severity of disease up to the limit where it has no longer detrimental effect on quality of life. Treatment choice should be according to the expectations and needs of each individual patient. To minimize the toxicity of any therapeutic, proper patient selection and appropriate monitoring is crucial. The administration of any therapeutic including topical therapy must be individualized. Every patient needs to be carefully evaluated in reference to disease severity, quality of life, and psychological status.

There should be proper assessment of disease severity and its impact to deliver high-quality health care with proper and regular measurement of treatment outcomes. Several tools have been described to assess severity of disease and treatment outcome, such as PASI (psoriasis area and severity index) score, Dermatology Life Quality Index (DLQI) score, Physician's Global Assessment, Psoriasis Disability Index, Psoriasis Life Stress Inventory, etc.^[2-6]

The guidelines developed by the American Academy of Dermatology (2009 evidence-based clinical practice), indicate that approximately 80 percent of patients affected with psoriasis have mild to moderate disease that can be managed with topical agents.^[7] Topical corticosteroids are the cornerstone for majority of patients with psoriasis, especially for those with limited disease and the wide availability of strengths and formulations favorably allow for versatility of use. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) advises that the use of topical steroids helps to improve the clinical symptoms associated with the disease, such as itching, but do not eliminate the disease. Phototherapy is reserved for widespread disease, or when the psoriasis is unresponsive to topical treatment. Systemic therapies are reserved for moderate to severe disease.^[8]

Topical Therapeutics in Psoriasis

Topical treatment includes a range of ointment, gel, paste, cream and scalp solutions. The main groups of topical agents for psoriasis are emollients, vitamin D analogues, topical corticosteroids (including combination preparations), coal tar preparations, dithranol, tazarotene (a topical retinoid) and keratolytics.

Usually the first form of treatment advised for the psoriasis is topical application of various medicaments. The main objective of the therapy is to achieve short-term suppression of symptoms and long-term modulation of disease severity. Moreover, topical therapy intends to improve quality of life with minimal adverse effects, however, there is no clear guidelines regarding the topical agent to be used in each type of psoriasis. Patients with mild disease (usually < 10% of their body surface) can often be managed topically. Coal tar preparations can be best used along with topical corticosteroids in rotation. Anthralin is more commonly used in short- term management of chronic plaque psoriasis. Vitamin D3 analogs are effective treatment for mild to moderate psoriasis and are well tolerated on the face and intertriginous areas without the use of corticosteroids. For moderate to severe psoriasis, medium to high potency corticosteroids can be used daily as first choice therapy.^[9]

Despite the various limitations, it is generally accepted that psoriasis affecting < 5% body surface area (BSA) is amenable to topical therapy.^[10] Topical therapy is safe and effective when used appropriately and has the benefit of limited systemic effects. When prescribing a topical therapy one must consider several factors, including patient motivation and understanding, vehicle of medicament, volume of treatment required and need for dressings.^[11]

Guidelines to use topical medications

1. Apply topical medicaments only to psoriasis lesions if possible to avoid irritating unaffected skin. A thin layer is generally sufficient. Wash your hands thoroughly after applying, unless your hands are being treated.
2. Always follow the instructions directed by your health care provider for topical application and consult your provider (or doctor) if you experience any unusual discomfort.
3. Do not apply topical medicaments around the eyes, genitals or other sensitive areas unless directed by your health care provider.

4. When prescribed multiple topicals, apply the topicals at different times of the day or as directed by your provider otherwise ask him in which order to apply them.
5. Do not overuse topical medications, as they can be absorbed into the body.
6. Pregnant or breastfeeding women should discuss the use of topical medications with their health care provider. Generally, topicals are not recommended unless the benefits outweigh the risks.
7. Do not occlude or cover up an application of a topical medication without discussing with your provider.
8. Consistent use of topicals is important for achieving treatment success.

Emollients (moisturizers)

Emollients provide a safe and useful adjunct in the treatment of psoriasis. Emollients help to moisturize dry skin. Optimization of skin hydration is universally recognized to improve the clinical condition of psoriasis.^[12] Emollients containing ingredients such as mineral oil are particularly helpful at relieving the dryness experienced with psoriasis. Emollients fill cavities and fissures of the skin with fat resulting in moisture retention and soft skin. They ease itching and dryness, reduces scaling, soften cracked areas and therefore, also help in the penetration of other topical treatments.^[13]

Diathralin (Anthralin)

Diathralin (anthralin in US), was introduced in 1916 to treat chronic plaque psoriasis. It is applied in a concentration of 0.1-1%, once a day and washed off thoroughly after a contact period of 10 minutes to one hour (average 30 minutes) i.e. a short contact. It is usually used in the patients with a small number of relatively large plaques than for widespread small lesions. It is a derivative of a traditional medicine chrysarobin and has been in use for a century. Dithranol causes skin irritation and brownish discoloration of skin. It is also used in combination with UV photo therapy to improve efficacy and to limit side-effects. Dithranol also reported to stains clothes.^[14]

Vitamin D3 Analogues

Calcipotriol, calcitriol and tacalcitol are analogues of vitamin D3. Calcitriol is the naturally occurring active form of vitamin D3. Vitamin D3 Analogues act by inhibiting epidermal cell proliferation and enhancing cell differentiation.^[15] Possibly the best known and most studied vitamin D3 analogue is calcipotriol/ Calcipotriene (Dovonex). Topical calcipotriol has been shown to be effective for the treatment of limited chronic plaque form psoriasis. These agents

may be combined with topical corticosteroids to improve response and reduce the dosage and duration of each treatment. They may also be combined with oral psoriasis therapies and phototherapy. The most significant clinical improvement is usually seen in the initial 6-8 weeks after initiating therapy. Calcitriol can modulate the dermal immune system through interfering with antigen presenting cells, regulatory T cell activation, cutaneous cytokine patterns and adaptive immunity.^[16]

Like topical corticosteroids, tachyphylaxis can occur after a few weeks of use of Vitamin D3 analogues. Therefore, rotational strategy is useful to ensure maximum therapeutic benefit. This involves rotating vitamin D with other treatments at every few weeks. Calcipotriol can be as effective as corticosteroids and has some reliable evidence that it can improve symptoms in mild to moderate psoriasis when combined with a topical corticosteroid, which is available as a single product for both plaque and scalp psoriasis. Calcitriol, another vitamin D analogue, is indicated for the topical treatment of mild to moderate plaque psoriasis.^[17-18]

Vitamin A analogues (Retinoids)

Tazarotene was the first retinoid (topical preparation) used to treat mild to moderate psoriasis. It should not be used on the face or skin folds or on large areas of the body, where it can cause irritation. It is reported to reduce inflammation and modulate the proliferation and differentiation of keratinocytes.^[19] It is potentially teratogenic and is contraindicated in women who may be/become pregnant.^[20]

Topical calcineurin inhibitors

Most common Calcineurin inhibitors include tacrolimus and pimecrolimus. They are large lipophilic molecules that may be used topically in the treatment of psoriasis. They block the T lymphocyte mediated signaling and cytokine production by inhibiting calcineurin.^[21] The main advantage of these drugs is the possibility of maintenance therapy for long periods eliminating the need for prolonged corticosteroids and their side effects. Their main indications are facial or inverse psoriasis that have not been responsive to weak or moderate strength topical steroids.^[22]

Coal tar

Coal tar was one of the first topical immunomodulators used for psoriasis treatment. One of the earliest references to its use was by the British Hospital for diseases of the skin in 1884.^[23] The possible mechanism of action is the reduction of mitotic rate in the epidermis

which further results in keratoplastic and anti-acanthotic action. They may also inhibit enzymes that contribute the pathogenesis of psoriasis.

Coal tar preparations were popular treatment for psoriasis at a time but have largely been replaced by topical corticosteroids due to their drawbacks which include its strong smell, irritation, staining of clothes and potential for causing photosensitivity.^[24]

Keratolytics

Keratolytics provide a useful adjunct to treatment where hyperkeratosis is symptomatic or limits the efficacy of other topical treatments. Options for therapy include salicylic acid, urea, propylene glycol and glycolic acids. These agents may be recommended to promote the shedding of psoriatic scales, theoretically facilitating greater penetration of topical medication.^[25-26] However, the need for such facilitation is unclear because normal scalp skin has low barrier function to percutaneous absorption of topical drugs and barrier function is further reduced in diseased skin.^[27]

In a study, salicylic acid 6% emollient foam was used twice-daily for 4 weeks in patients with scalp psoriasis. The study revealed 60% of subjects were either completely cleared or almost cleared with approximately 90% improvement in their psoriasis by fourth week and no adverse events were reported.^[28]

Topical steroids

Topical steroids are the most used medication in the treatment of psoriasis. Corticosteroids were discovered in 1935 as compound E or cortisone. Finally, psoriasis was included in the list of skin diseases treatable with hydrocortisone in 1955 and a breakthrough occurred in the topical treatment of psoriasis with the introduction of topical steroids in 1960s. Although corticosteroids effectively suppress the psoriasis in short term, they are associated with relapse or vigorous rebound on withdrawal. Efficacy of steroid is directly related to the skin penetration of its molecules and the rate of absorption is influenced by its chemical structure.^[29] The therapeutic effect of topical steroid is under the stratum corneum which is demonstrated by antimetabolic effect in the skin lesions of psoriasis. Topical corticosteroids have anti-inflammatory, immunosuppressive, antimetabolic and anti-proliferative activities. Therapy is usually started with a potent steroid (clobetasol propionate or betamethasone dipropionate) applied once or twice daily.^[30]

Potent topical gluco-corticosteroids leads to anti-inflammatory effects when first applied but with subsequent applications their therapeutic action rapidly diminishes, which is known as tachyphylaxis.^[31] However, after a rest period of a few days, the same initial beneficial response may be produced again, but this will also disappear if the steroid is again continued topically. Therefore, steroids should be used for 2 to 3 weeks and then tapered with the intention of discontinuation.

Prolonged topical steroids use can cause skin atrophy, hair growth and hypo pigmentation. Chronic usage also results in thinning and telangiectasia of the skin. Systemic effects (such as Cushing's syndrome and suppression of the hypothalamic-pituitary axis) may occur if there is chronic usage on large areas of the body.^[32]

Clobetasol propionate is a super high-potency glucocorticosteroid, initially approved for treatment of steroid-responsive dermatosis. Clobetasol propionate is traditionally formulated in an ointment base for treatment of psoriasis. Currently several novel formulation of clobetasol propionate are also available such as spray, foam, lotion and shampoo. Application of these may resulted in improved convenience and acceptance in many patients with similar efficacy, safety, and tolerability as the traditional ointment and cream formulations.^[33]

Mometasone furoate is a potent synthetic glucocorticoid, which is commonly used in dermatological conditions. It is available as cream, ointment and lotion formulations for the treatment of patients with atopic dermatitis, seborrhoeic dermatitis, scalp psoriasis and psoriasis vulgaris. Mometasone demonstrates greater anti-inflammatory activity and a longer duration of action than betamethasone and also exhibit low potential to cause adverse systemic effects such as suppression of the hypothalamic-pituitary-adrenal (HPA) axis.^[34]

Betamethasone dipropionate is commonly formulated as a gel. It is synthetic fluorinated corticosteroid with moderate potency and is commonly used in combination with vitamin D3 analogues. Several attempts have been made to increased betamethasone dipropionate skin permeation by encapsulating in liposomes. Betamethasone valerate (BMV) is also available as a foam formulation containing 0.12% betamethasone valerate for use as a treatment for psoriasis affecting the scalp and non-scalp regions of the body.^[35-36]

Halobetasol is a synthetic tri-halogenated corticosteroid structurally similar to clobetasol propionate but with an additional fluorine atom. Halobetasol propionate is a high potency corticosteroid available as 0.05% ointment and cream.^[37]

Intralesional corticosteroid therapy

Triamcinolone hexacetonide (5 mg/mL) or triamcinolone acetonide (10 mg/mL) can be infiltrated intra-dermally into localized psoriatic lesions by needle injection. It is a valuable technique in troublesome, small, resistant lesions on the back of hands, especially the knuckles, intensely pruritic small plaques or lichenoid lesions. The effect is long-lasting and repetition of the injection may be unnecessary for several months. In treatment of psoriasis of fingernails, the nail fold can be injected, but results are disappointing and the procedure may be painful.^[38]

Due to the nature of topical application, all products are minimally exposed to the systemic circulation. Ointment is oil based and has been theorized to be the most effective vehicle for psoriasis due to its occlusive nature and moisturizing ability. Preference of the ointment is typically low since it is greasier and messier than other available vehicle choices.

Creams are oil in water emulsions which tend to be less greasy than ointments and may be more appealing cosmetically. Gels are similar to creams but are colorless and contain alcohol. They absorb rapidly, but can have a drying effect and cause a burning sensation, which may be intolerable to those with sensitive skin. They are also flammable due to the alcohol. Solutions are water based and can have a drying effect. They are easier to apply to larger areas such as the scalp.^[39]

According to the psoriasis guidelines of American association of dermatology (AAD) 2009, the topical corticosteroids have been the cornerstone of treatment for patients with mild to moderate disease, but due to limitations of a short duration of treatment and risks involved with long term use, they are not the choice for long term management of psoriasis. These guidelines recommend the choice of therapy to be based on an individualized approach with leaning toward improving patient adherence (especially since the adherence to treatment is poor due to the intolerance to the medications), lack of response, poor choice of vehicle, and fear of adverse effects. In addition these guidelines, AAD also recommended the use of the topical medications to patients with mild to moderate psoriasis and the systemic medication to severe form.^[40-41]

The complete clearance of lesions is often not a realistic goal with topical therapy but eventually remission can be reached. Studies suggest that adherence with topical treatment in psoriasis is poor. Patients requiring ongoing treatment with topical agents containing high

potency corticosteroids should be monitored regularly for adverse effects and steroid sparing concomitant treatments should be introduced. The rotation of a non-steroidal topical agent following initial treatment is indicated.

The third section of six part series of guidelines (AAD, 2009) discusses the use of topical medications for the treatment of psoriasis. The guidelines focus on efficacy and safety, recommendations for the use of topical corticosteroids as well as combination therapy. The patients with localized psoriasis can be treated with topical agents, which generally provide a high efficacy to safety ratio. Topical agents may also be used adjunctively in patients with more extensive psoriasis who are undergoing therapy with either ultraviolet light, systemic or biologic medications. However, the use of topical agents as monotherapy in the generalized form of the disease or in the setting of limited, but recalcitrant, disease was not recommended.^[42]

Hurdles in the development of topical medications for psoriasis

Various hurdles encountered in the development of topical medication for psoriasis due to unique nature of drug delivery across the skin. The hurdles are as follows.^[43-44]

1. Psoriatic lesions can have both thickened and markedly thinned epidermis; this heterogeneity in the skin morphology can increase the variability in drug permeation and systemic absorption, thus increasing challenges in formulation development.
2. A significant number of psoriasis patients feel that the current therapies are either not sufficiently efficacious or aggressive. Hence, a primary challenge is to develop new therapies with once daily application and show quick response, such as within the first four weeks of treatment.
3. Effective management of psoriasis frequently necessitates combining therapies in order to achieve optimum response while minimizing any side effect. Thus any new topical therapy should have appropriate safety and efficacy when used in combination with another topical medication, systemic therapy and/or phototherapy.
4. In order to increase patient adherence to therapy, new topical formulations should have appropriate cosmetic elegance such as ease of use, no or minimal staining potential on clothing and bedding, quick absorption on application and being less greasy.
5. Formulations which can be used on many areas of the body including hair-bearing sites are preferred as patients often have psoriasis plaques in multiple areas.

6. Due to the availability of a wide variety of therapies and presence of generic products in the market, competitive cost of any new medication is paramount in influencing physician's and patient's choice for product.

CONCLUSION

Psoriasis is a common chronic condition and has been shown to significant influence on patient's quality of life. Topical treatment remains the mainstay of therapy in psoriasis, with 70-80 per cent patients with psoriasis responding adequately to topical treatments. Vitamin D3 analogues such as calcipotriol alone and in combination with a corticosteroid are increasingly preferred as first line topical therapy by patients for convenience and ease of use. Despite the introduction of photo-therapy & photo-chemotherapy, traditional systemic drugs and biological agents, topical medications continue to play an essential role in the therapeutic field of psoriasis. Topical therapies are the mainstay for mild disease either as monotherapy or in combination and are also commonly used in conjunction with phototherapy, traditional systemic agents, or biologic agents for moderate to severe disease. Further research and development in the field of topical immuno-modulators will hopefully result in the design of even more effective drugs, with increased specificity of action and fewer side effects.

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