

## Topical Therapies in Psoriasis

### Abstract

Topical therapy as monotherapy is useful in psoriasis patients with mild disease. Topical agents are also used as adjuvant for moderate-to-severe disease who are being concurrently treated with either ultraviolet light or systemic medications. Emollients are useful adjuncts to the treatment of psoriasis. Use of older topical agents such as anthralin and coal tar has declined over the years. However, they are cheaper and can still be used for the treatment of difficult psoriasis refractory to conventional treatment. Salicylic acid can be used in combination with other topical therapies such as topical corticosteroids (TCS) and calcineurin inhibitors for the treatment of thick limited plaques to increase the absorption of the latter into the psoriatic plaques. Low- to mid-potent TCS are used in facial/flexural psoriasis and high potent over palmoplantar/thick psoriasis lesions. The addition of noncorticosteroid treatment can also facilitate the avoidance of long-term daily TCS. Tacrolimus and pimecrolimus can be used for the treatment of facial and intertriginous psoriasis. Tazarotene is indicated for stable plaque psoriasis usually in combination with other therapies such as TCS. Vitamin D analogs alone in combination with TCS are useful in stable plaques over limbs and palmoplantar psoriasis. Topical therapies for scalp psoriasis include TCS, Vitamin D analogs, salicylic acid, coal tar, and anthralin in various formulations such as solutions, foams, and shampoos. TCS, vitamin D analogs, and tazarotene can be used in the treatment of nail psoriasis.

**Keywords:** Psoriasis, therapeutic guidelines, topical therapy

### Introduction

In India, the prevalence of psoriasis varies from 0.44%–2.8%.<sup>[1]</sup> The majority of these patients have mild-to-moderate disease and can be treated with topical agents which provide potential therapeutic efficacy and limit the adverse effects of the systemic treatment to the target tissue.

### Aim of Therapy

The aim of the therapy is to minimize the extent and severity of psoriasis to the point at which it is no longer detrimental to a patient's quality of life.

### Indications

Topical therapy is the treatment of choice in patients with psoriasis affecting <10% body surface area (BSA) (mild psoriasis).<sup>[2]</sup>

It can also be used for psoriasis affecting sensitive areas such as the face, flexures, and genitals.

Topical agents are also used as adjuvant for:

- Psoriasis affecting >10% BSA (moderate/severe psoriasis) on

ultraviolet (UV) light or systemic medications

- Refractory palmoplantar or scalp psoriasis.

### Factors Which Influence Topical Therapy

#### Patient factors

Treatment regimens must be individualized according to the patient's age, sex, occupation, understanding, and the available resources.

#### Disease factors

Treatment also depends on the site of the lesions and their extent and severity. Assessment of severity should include the patient's own perception of disability, the need for treatment, and an objective assessment of extent and severity.

#### Vehicle

The choice of vehicle can significantly alter the use and penetration of medications, and hence the therapeutic effect. There is a vast array of vehicles including creams,

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gels, solutions, foams, sprays, shampoos, and lotions. Different vehicles are indicated for different body sites. Scalp is commonly involved in psoriasis and requires gel, solutions, or foams that are not as messy as ointments and creams. Elsewhere, patients may prefer a less greasy preparation such as a cream during the daytime, and an ointment which is more effective but less cosmetically appealing at night.

### Occlusion

Occlusive therapy, in which the skin is covered, often with a plastic membrane, enhances the penetration of topical agents such as corticosteroids. The occlusive dressings trap heat and moisture, hydrating and macerating the skin and forcing the medication through the plaques.<sup>[3-5]</sup>

### Combination therapy

Combination therapy may be indicated when monotherapy fails, for example, the combination of super potent steroids and calcipotriene.<sup>[6,7]</sup> However, when using multiple topical agents, it is important to be aware of possible compatibility issues, for example, salicylic acid inactivates calcipotriene.<sup>[8]</sup> On the other hand, anthralin requires salicylic acid for its chemical stability.<sup>[9]</sup> When it is desirable to use multiple topical agents, patients may be instructed to apply the various medications at separate times throughout the day.

Topical agents can be used intermittently or continuously. More potent agents must be used on a short-term basis to allow for response, and then patients should be instructed to use these agents intermittently for long-term management. This strategy may reduce the risk of side effects.

Alternatively, patients who require continuous topical therapy should be instructed to use the least potent agent that allows for disease control or be transitioned to a topical agent that is associated with the lowest long-term risk.

All patients on topical therapy should be examined regularly to look for the development of side effects at the earliest.

### Adherence to Therapy

Adherence to topical treatment is a major issue, being generally poor in the majority of the patients. In compliance studies, 39% of the patients admitted to nonadherence with topical therapy.<sup>[10]</sup> Adherence has been seen to improve with simple regimens and once a day therapy. Moreover, realistic treatment outcomes should be discussed with patients, and they should be encouraged to participate in decision making.

### Emollients and Moisturizers

Emollients form the backbone of therapy for psoriasis. They are a valuable first-line treatment because dry skin is common in psoriasis and adds to its irritability.

### Mechanism of action

Moisturizers help in normalizing hyperproliferation, differentiation, and apoptosis. They have anti-inflammatory effects in addition to improving barrier function. This helps in combating the stresses generated in the skin and Koebner's phenomenon.<sup>[11]</sup>

Hence, emollients moisturize dry skin, reduce scaling, ease itching, soften cracks, and improve penetration of other topical agents.<sup>[12]</sup> They may also slow down the rate of epidermal turnover.

### Efficacy

Emollients do not work as a monotherapy but as an adjuvant to topical/systemic therapy.

- There are two randomized, placebo-controlled trials of aloe vera gel for the treatment of mild-to-moderate psoriasis with one showing better efficacy compared to placebo<sup>[13]</sup> and the other showing no benefit over placebo<sup>[14]</sup>
- It has been reported for chronic plaque psoriasis that water-in-oil emollients are useful as steroid-sparing agent.<sup>[15]</sup> The hydration of the stratum corneum leads to an enhanced delivery of topical corticosteroids (TCS).

### Vehicles and preparations

Emollients come in many different forms such as creams, ointments, lotion, bath oils, and soap substitutes. Creams and ointments are preferable to lotions. They tend to be thicker, more occlusive, and therefore more effective.<sup>[15]</sup> Ointments are more suited for extra dry, thickened, or brittle skin and can be used at night. Lighter, less greasy creams or lotions are ideal for daytime use. Creams, ointments, or lotions should be used liberally and frequently such that the skin does not dry out (dehydrating). The commonly used emollients are petroleum jelly, liquid paraffin, and mineral oils.

### Adverse effects

Emollients can cause a few side effects such as irritant dermatitis, allergic contact dermatitis, fragrance allergy, stinging, cosmetic acne, and pigmentary disorders.<sup>[16]</sup>

There are no contraindications to the use of emollients. These are considered to be safe during pregnancy and lactation as well as for pediatric use.

### Anthralin (Dithranol)

Over the years, anthralin has been shown to be one of the most effective topical treatments of stable plaque psoriasis. It may be used as a Short contact anthralin therapy (SCAT) for the treatment of localized, scaly plaques of psoriasis on the body or the scalp that have not cleared with other treatments.

### Mechanism of action

Anthralin reduces keratinocyte proliferation, prevents T-cell activation, and restores cell differentiation, probably through mitochondrial dysfunction.<sup>[17]</sup> In addition, production of free radicals may contribute to its effect.<sup>[18]</sup>

### Modes of application of anthralin

Although anthralin has been used as an overnight therapy, we recommend that it be used only as SCAT in which high concentration of anthralin, 1% or greater, is applied for approximately 20 min to 1 h before removal.<sup>[19]</sup>

In another regimen, anthralin in a concentration of 1% or greater is applied for 5 min on the 1<sup>st</sup> day. Daily applications continue with increases up to 5 min every other day until patients develop mild irritation. The period of application is then maintained until clearing.

### Efficacy

There is limited placebo-controlled trial data. In a systematic review of topical preparations for the treatment of psoriasis, it was found that dithranol reduced psoriasis severity scores at 4–8 weeks significantly more than placebo.<sup>[20]</sup> Short contact (30 min) and overnight therapy with 1%, 2%, and 3% dithranol ointment have shown similar efficacy, suggesting SCAT to be more convenient and practical.<sup>[21]</sup> Anthralin, similar to monotherapy, appears to have lower efficacy than more potent TCS or Vitamin D derivatives.<sup>[22]</sup> Other randomized controlled trials have found that Vitamin D analogs are equally effective as short contact dithranol regimen but with better tolerability and acceptability of Vitamin D analogs.<sup>[23,24]</sup>

### Adverse effects

The most common side effect of anthralin is skin irritation, which is dose related. Anthralin also stains lesional and adjoining skin, hair, nails, clothing, and other objects, with which the patients come into contact.<sup>[25]</sup> Attempts to reduce these using low concentrations SCAT and concomitant steroid therapy have been only partially successful. Triethanolamine applied after the removal of anthralin, prevents staining and irritation by neutralizing any anthralin residue remaining on the skin.<sup>[26]</sup> Chlorine bleach can be used to remove stains from household items.<sup>[27]</sup> If the psoriatic plaques are well-defined, the surrounding normal skin can be protected by the use of an agent such as zinc oxide paste. It should be applied with caution to the face and intertriginous areas due to the risk of skin irritation.

No systemic toxicity has been reported even following long-term application of anthralin. Anthralin is pregnancy Category C.

For children: Use with caution.

Salicylic acid is frequently added to improve the stability of anthralin and to increase its penetration and efficacy.<sup>[28]</sup>

### Preparations

1. Derobin ointment containing dithranol 1.15%, coal tar solution 5.3%, salicylic acid 1.15%, and petrolatum base
2. Micanol is a 1% anthralin formulation in a temperature sensitive vehicle (microcapsules).<sup>[29]</sup> It is removed by washing with cold water which leads to re-crystallization. It is effective in short and long contact regimens. It is particularly useful for scalp psoriasis
3. New formulations in emulsifying ointment base with 0.1% w/w ascorbyl palmitate as an anti-oxidant are stable for up to 52 weeks<sup>[30]</sup>
4. Dithranol, in an emulsifying oil base (bio-wash oil), is useful for scalp psoriasis<sup>[31]</sup>
5. Liposomal dithranol (lipogel) is an effective formulation with less irritation and staining.<sup>[32]</sup>

### Coal Tar

Coal tar is frequently used as a part of an inpatient or daily dressing regimen. Its use in conjunction with UVB, the Goeckerman regimen, is well recognized.<sup>[33]</sup> Coal tar probably suppresses DNA synthesis, thereby reducing the hyperproliferation of keratinocytes.<sup>[34]</sup>

### Efficacy

The success of coal tar has been demonstrated on chronic plaque psoriasis, palmoplantar psoriasis, and scalp psoriasis. Most chronic plaques improve after 1 month and patients remain in remission for longer than that with other psoriasis topical treatments.<sup>[35]</sup>

- A recent Cochrane review of efficacy of coal tar preparations supports the use of coal tar products in the treatment of psoriasis, although the level of evidence is not strong. Coal tar is well tolerated with a few side effects.<sup>[36]</sup>
- Coal tar was as effective as calcipotriol after 12 weeks of treatment in a prospective study, however, Vitamin D analog was better tolerated and had a faster onset of action.<sup>[37]</sup>
- Similarly, Khandpur *et al.* compared the efficacy of coal tar–salicylic acid ointment versus calcipotriol/betamethasone dipropionate (BMD) ointment and concluded that both the treatment modalities were comparable in efficacy at the end of 12 weeks, although the calcipotriol/BMD ointment had quicker onset of action.<sup>[38]</sup>
- Other comparative studies have found calcipotriol superior to coal tar treatment.<sup>[39]</sup>

### Side effects

The use of tar has waned due to its poor side effects profile and superior efficacy of alternative topical therapies.<sup>[40]</sup>

Adverse effects of coal tar include odor, staining, irritant contact dermatitis, erythema, stinging, folliculitis, and formation of keratoacanthomas.<sup>[41]</sup>

Occupational coal tar exposure is a recognized carcinogen. However, there is no evidence of carcinogenesis reported in patients with psoriasis who have had treatment with coal tar.<sup>[42,43]</sup>

Treatment with PUVA and coal tar is not recommended due to the risk of skin cancer.<sup>[43]</sup>

Coal tar (Category C) may be used during pregnancy.<sup>[44]</sup>

Coal tar should be used with caution in the pediatric population.

### *Newer formulations of coal tar*

Recently new formulations of coal tar, ranging from 1% to 15% have been developed. They are claimed to be nonstaining, nonodorous, and easily spreadable. Their efficacy is superior to conventional coal tar preparations and equal to topical ultrapotent steroid preparations.<sup>[45-47]</sup>

### *Salicylic Acid*

Salicylic acid is a topical keratolytic agent that has been used for many years in the topical treatment of psoriasis. It can be used in combination with TCS and calcineurin inhibitors to increase the absorption of the latter into the psoriatic plaques.

### *Mode of action*

Salicylic acid leads to desquamation of corneocytes through two pathways. It reduces intercellular cohesiveness of the horny cells by dissolving the intercellular cement material. Moreover, it reduces the pH of the stratum corneum, thereby increasing hydration and softening.<sup>[48]</sup>

### *Efficacy*

While there are no placebo-controlled studies verifying the efficacy and safety of salicylic acid used alone, salicylic acid is often combined with other topical therapies, including TCS<sup>[49]</sup> and immunomodulators<sup>[50]</sup> in the therapy of psoriasis. Salicylic acid significantly increases the penetration rate of TCS because of its keratolytic effects.<sup>[49]</sup>

Steroid-salicylic acid combination can be used as first line of treatment on thick, scaly plaques.

Salicylic acid can be applied to areas with thick stratum corneum including palms, soles, and scalp. It can also be used on the trunk. Its use should be avoided on genitals, the mucous membrane, and the eyes.

Tiplica *et al.* found that the combination of mometasone furoate (0.1%) and salicylic acid (5%) was more effective than monotherapy with mometasone furoate (0.1%).<sup>[49]</sup>

The addition of salicylic acid to dithranol formulations improves the clinical efficacy of dithranol because of the antioxidant properties of salicylic acid.<sup>[51]</sup>

It can be applied as a paste or in creams, ointments, and lotions in concentration of 2%–6%.

### *Adverse effects*

The major problem in the topical treatment of psoriasis with salicylic acid is the potential chronic or acute systemic intoxication with the symptoms of oral mucosa burning, frontal headache, central nervous system symptoms, metabolic acidosis, tinnitus, nausea, and vomiting.<sup>[52,53]</sup>

These symptoms may occur in the topical treatment of large body surfaces, especially in children.<sup>[54,55]</sup> Even lethal cases are reported;<sup>[56]</sup> therefore, a concentration greater than 10% and an application on larger surfaces, especially in children, are not suitable. Salicylic acid should not be applied to more than 20% of the BSA.

If larger surfaces require a salicylic acid treatment for initial keratolysis, a sequential treatment is useful (e.g., affected areas in the upper part of the body at night and the lower part of the body in the morning). Careful clinical monitoring helps to avoid salicylic acid intoxication.

It should be noted calcipotriol is inactivated by salicylic acid.<sup>[57]</sup>

Salicylic acid blocks UV light, and therefore should be applied after phototherapy.<sup>[48]</sup>

### *Pregnancy and children*

Salicylic acid can be safely used for localized psoriasis in pregnancy; however, because of a greater risk of systemic absorption and toxicity, salicylic acid should be avoided in children.

### *Topical Immunomodulators*

#### *Calcineurin inhibitors*

Calcineurin inhibitors are approved for use in mild-to-moderate atopic dermatitis only; any use in psoriasis is off label.

#### *Mechanism of action*

Calcineurin inhibitors inhibit the action of calcineurin phosphatase and block the production of inflammatory substances that are thought to be important in causing skin lesions in psoriasis.<sup>[58]</sup>

There are two topical preparations of calcineurin inhibitors, namely, tacrolimus ointment (0.03% and 0.1%) and pimecrolimus cream (1%).

#### *Tacrolimus and pimecrolimus*

Neither tacrolimus ointment<sup>[59]</sup> nor pimecrolimus cream<sup>[60]</sup> appears to be effective for treating plaque-type psoriasis when simply applied as commercially available preparations. This is probably because of large molecular size and the inability to penetrate thick, psoriatic plaques. However, the penetration can be enhanced by occlusion<sup>[60]</sup> or by combining these agents with salicylic acid.<sup>[50]</sup>

## Efficacy

A recent review of the efficacy of topical calcineurin inhibitors (TCIs) in psoriasis has concluded that topical tacrolimus (0.1%), and to a lesser extent, pimecrolimus (1%) have efficacy in the treatment of psoriasis. These are safe and effective in patients with facial, intertriginous, and genital psoriasis.<sup>[61]</sup>

However, they are less potent than 0.005% calcipotriol or 0.1% betamethasone valerate.<sup>[62]</sup>

Newer vehicle of topical tacrolimus, a 0.3% gel and 0.5% cream, have been developed to improve its penetration into thick psoriatic plaques.<sup>[63]</sup>

## Adverse effects

The most common adverse event reported with the use of tacrolimus and pimecrolimus is a stinging sensation, which is usually transient.<sup>[61]</sup> Irritation is more significant with tacrolimus than pimecrolimus.

There is a theoretical risk of cancer with long-term use of TCI, and a black box warning has been added to the labels of these medications.<sup>[64]</sup> As a result, new Food and Drug Administration (FDA) recommendations state that topical immunomodulators should not be used as long-term treatment, over large surface areas, or in children under the age of 2 years.

## Use of calcineurin inhibitors in pregnancy and pediatric population

Both topical tacrolimus and pimecrolimus have been labeled Category C, but are generally not considered teratogenic due to their low systemic absorption.<sup>[65]</sup> Both these medicines are found in human milk, and hence are not recommended for nursing mothers.

Topical tacrolimus (0.03%) ointment and topical pimecrolimus cream are approved for patients as young as 2 years with atopic dermatitis. There is minimal evidence regarding the safety and efficacy of these medications in young patients with psoriasis. A recent single-center, open label trial has demonstrated that tacrolimus ointment is an effective treatment for psoriasis on the face or intertriginous areas in children with minimal side effects.<sup>[66]</sup>

## New calcineurin inhibitor

### Sirolimus

It is a newly developed topical immunomodulator. It has recently been investigated as a possible treatment for chronic plaque psoriasis.<sup>[67]</sup>

## Topical Retinoids

### Tazarotene

Tazarotene, a Vitamin A derivative, is the first synthetically developed retinoid indicated for the topical treatment of psoriasis. It is available as a gel or cream at concentration

of 0.1% or 0.05%. Tazarotene is indicated for stable plaque psoriasis usually in combination with TCS and calcipotriene. It has been demonstrated to be an effective maintenance therapy for psoriasis. Tazarotene under occlusion is also effective in the treatment of nail psoriasis.

## Mechanism of action

Tazarotene selectively binds to  $\beta$  and  $\gamma$  retinoic acid on the cell membrane of keratinocytes and is then transported to the nucleus, altering transcription of genes in keratinocytes. This results in reduced epidermal hyperproliferation, normalizing keratinocyte differentiation, and decreasing inflammation.<sup>[68]</sup>

## Efficacy

- In a recent study, tazarotene 0.1% and 0.05% cream applied daily for 12 weeks was found to be more effective than vehicle in plaque psoriasis.<sup>[69]</sup>
- Tazarotene (0.1% and 0.05%) has been found to be as effective as flucanide with greater remission rate and more irritation than the latter.<sup>[70]</sup>
- In a recent observer-blinded, randomized controlled trial conducted in India, 0.1% tazarotene cream was as effective as clobetasol propionate for palmoplantar psoriasis.<sup>[71]</sup>
- Its efficacy has been demonstrated to be comparable to calcipotriene 0.005% ointment<sup>[72]</sup> and 5% coal tar ointment.<sup>[73]</sup>
- The combination of tazarotene with mometasone demonstrated greater efficacy and more rapid and sustained improvement than corticosteroids monotherapy.<sup>[74]</sup>
- Once daily application of 0.1% tazarotene for 12–24 weeks has been shown to improve nail psoriasis including onycholysis, hyperkeratosis, pitting, and salmon patches.<sup>[75]</sup>

## Adverse effects

The most common side effect of tazarotene is localized irritation.<sup>[69]</sup> The use of cream, low concentration, alternate day application and short contact (30–60 min) application may help alleviate such symptoms.<sup>[76]</sup> Concomitant use of TCS may also minimize symptoms.

Tazarotene must not be used in sensitive areas such as the face, flexures and genitals.<sup>[77]</sup>

The FDA has issued a caution regarding the use of tazarotene and exposure to sunlight, and patients are advised to use sunscreens when using tazarotene. When it is combined with phototherapy, the dosimetry might need to be lowered to prevent skin burning.

## Use of tazarotene in pregnancy and children

Tazarotene is contraindicated in pregnancy, Category X, because of the theoretical risk of teratogenicity.<sup>[65]</sup> Children tolerate topical retinoids very well. Topical retinoids

are, therefore, considered safe and efficacious in the pediatric populations, although no specific trials have been conducted in children and it remains an off-label use of the medication.

### **New retinoids**

#### **Bexarotene**

Bexarotene gel is being studied as a potential treatment for psoriasis. It selectively binds nuclear retinoid X receptor.

Bexarotene gel 1% has been found to be effective in treating mild-to-moderate plaque psoriasis as monotherapy<sup>[78]</sup> as well as in combination with narrowband UVB therapy.<sup>[79]</sup>

### **Topical Corticosteroids**

TCS are universally used in the management of all grades of psoriasis. They are used as monotherapy when the disease is mild and as a complement to systemic therapy in patients with moderate-to-severe psoriasis.

#### **Mechanism of action**

Corticosteroids are vasoconstrictive, antiproliferative, anti-inflammatory, and immunosuppressive. They bind to intracellular corticosteroid receptor and regulate gene transcription of numerous genes, particularly those that code for proinflammatory cytokines.

#### **Selecting potency of topical corticosteroids**

While selecting the potency of corticosteroids and its vehicle, one should take into consideration the disease severity, the site being treated, patient preference, as well as the age of the patient. Penetration correlates inversely with the thickness of the stratum corneum<sup>[80]</sup> and is greatly increased on areas such as the scrotum and face [Table 1].<sup>[81]</sup>

Potent and superpotent TCS may be used for stubborn, thick, and chronic plaques.

#### **Efficacy**

Clinical efficacy of Class I TCS such as clobetasol and halobetasol is well established in the treatment of plaque psoriasis.<sup>[82,83]</sup> Treatment is generally twice a day for approximately 2 weeks followed by an intermittent dosing regimen to preserve remission. Similarly, midpotent TCS such as fluticasone propionate has also been found to be effective in plaque psoriasis.<sup>[84]</sup>

Different regimens have been tried for maintenance therapy with TCS. Three consecutive applications (12 h apart) once a week therapy with BMD ointment has been used for maintenance of remission.<sup>[85]</sup> Another maintenance regimen of clobetasol propionate twice weekly achieved remission for an average of 4 months in 75% of treated patients.<sup>[86]</sup>

TCS in the form of lotions, solutions, and foams are effective in scalp psoriasis.<sup>[75,87,88]</sup>

Potent topical steroids such as clobetasol propionate can be used for the treatment of psoriasis involving nail bed and/or nail matrix.<sup>[75]</sup>

### **Limitations**

TCS are often used for longer period. This can lead to tachyphylaxis.

The side effects of TCS<sup>[89]</sup> include skin atrophy striae, telangiectasia, or secondary infection. Therefore, potent TCS should not be used on the face or intertriginous sites. Systemic adverse events occur when TCS are used for prolonged periods of time or at doses higher than commonly prescribed. Prolonged use of potent TCS may result in its significant systemic absorption which can lead to HPA axis suppression, Cushing's syndrome, and hyperglycemia.

Another possible concern is the rebound phenomenon after abrupt discontinuation of TCS.

TCS usage in higher doses can lead to a pustular flare of psoriasis on their discontinuation.

### **Topical corticosteroids use in pregnancy and in pediatric population**

TCS are labeled as pregnancy Category C.<sup>[90]</sup> Their safety in breastfeeding is unknown.

Infants and young children are at greater risk for side effects due to their higher skin surface to body mass ratio. Both growth retardation and suppression of the HPA axis have been documented in children more frequently than in older population.<sup>[91]</sup> As a result of systemic absorption, regular assessment of growth in children using TCS for long-term is recommended.

### **New vehicle formulations for topical corticosteroids**

New formulations have been developed in the form of spray, shampoos, and foams in an effort to enhance the delivery of TCS. All of the newer topical clobetasol propionate formulations produce clearing of psoriasis for a large proportion of patients within 2–4 weeks with response, safety, and tolerability rates that are at least

**Table 1: Selecting potency of topical corticosteroids and vehicle according to the site involved**

Site	Potency of TCS	Vehicle
Face	Low and medium potency	Creams
Intertriginous areas	Low and medium potency	Creams
Trunk and extremities	Moderate to potent	Ointment, spray, foam
Palms and soles	Potent to superpotent	Ointment
Scalp	Moderate to high	Solution, lotion, foam, gel, shampoo

TCS: Topical corticosteroids

comparable to the conventional TCS creams and ointments. The spray and the foam may have an important role in the treatment of widespread plaque psoriasis while the shampoo and the foam would be useful in scalp psoriasis.<sup>[92,93]</sup> Eight percent clobetasol propionate in a nail lacquer vehicle has been formulated for treatment of nail psoriasis.<sup>[91]</sup>

### Vitamin D Analogs

Vitamin D analogs provide a useful adjunct in the treatment of chronic plaque psoriasis. They are also useful in the treatment of nail psoriasis and chronic plaque psoriasis of the scalp. It should be used under occlusion for nail psoriasis. Synthetic Vitamin D analogs have been developed (by modification of the side chain) to enhance the antipsoriatic effect of Vitamin D<sub>3</sub> and reduce their hypercalcemic action (because they are rapidly transformed into inactive metabolites).

#### Mechanism of action

Vitamin D analogs bind to the intracellular Vitamin D receptor which then binds to and regulates the genes involved in epidermal proliferation, inflammation, and keratinization.<sup>[94]</sup>

There are three Vitamin D analog preparations available to treat psoriasis, namely, calcipotriene (calcipotriol in Europe), calcitriol, and tacalcitol.

#### Calcipotriene

It is a synthetic Vitamin D analog available as 0.005% (5 mg/g) cream, ointment, and scalp lotion. Although it is as potent as 1, 25 dihydroxycholecalciferol in the regulation of cell proliferation and differentiation, it is at least 200 times less potent in its effects on calcium metabolism.<sup>[94]</sup>

#### Efficacy

It has similar efficacy to Class 2 and 3 TCS but has relatively fewer side effects. In comparison to superpotent TCS, calcipotriene has delayed onset of action but results in longer disease-free interval.<sup>[95]</sup> As monotherapy, the maximal response usually requires 2 months of therapy.<sup>[96]</sup>

- The Cochrane systematic review provided evidence that twice daily calcipotriene is a safe and effective treatment for plaque psoriasis<sup>[97]</sup>
- It is more effective than other Vitamin D analogs (tacalcitol or calcitriol), short contact dithranol therapy,<sup>[97]</sup> and 15% coal tar<sup>[39]</sup>
- Calcipotriene solution has been found to be effective for the treatment of scalp psoriasis<sup>[98]</sup>
- Combination of the calcipotriene and TCS in ointment and solution forms has proven superior to either agent used alone<sup>[99]</sup>
- A new calcipotriene/BMD aerosol foam formulation has been found to be safe and effective in patients with extensive psoriasis vulgaris.<sup>[100]</sup>

#### Calcitriol

It is a synthetic form of the active metabolite of Vitamin D.<sup>[96]</sup> It is available as an ointment only (3 mg/g).

#### Efficacy

Multicenter and randomized clinical trials have demonstrated long-term safety and efficacy of calcitriol.<sup>[101]</sup> It is less potent than BMD, 0.05% but induces longer remission than the latter.

#### Tacalcitol

It is a synthetic Vitamin D analog available as 4 mg/g ointment and lotion, applied once daily.

#### Efficacy

Clinical studies have shown tacalcitol ointment to be a safe and effective long-term treatment for chronic plaque psoriasis with no systemic side effects and good tolerability in sensitive areas.<sup>[102]</sup> It is, however, less potent than calcipotriene.<sup>[103]</sup> The combination with clobetasol propionate in lacquer for the treatment of nail psoriasis where tacalcitol ointment under occlusion was applied twice daily on weekdays and the steroid lacquer on weekends has been found to be effective.<sup>[75]</sup>

#### Adverse effects

Vitamin D analogs are relatively safe with few side effects. The most common adverse effect is skin irritation on or around the psoriasis plaques.<sup>[102]</sup> Face and intertriginous areas are especially prone to irritation. Calcitriol and tacalcitol have a better tolerability on sensitive areas as compared to calcipotriene, and therefore serve as better options in these areas.<sup>[102,104]</sup>

Systemic side effects such as hypercalcemia, hypercalciuria, and parathyroid hormone suppression are very rare if the maximum dose is not exceeded: 100 g/week for calcipotriene, 210 g/week for calcitriol, and 70 g/week for tacalcitol.<sup>[105]</sup>

Calcitriol may have greater effects on serum calcium in comparison to other analogs.<sup>[106]</sup>

Vitamin D analogs are contraindicated in patients already suffering from hypercalcemia. Patients with renal impairment need to be observed carefully.

Calcipotriene is a relatively unstable molecule that is inactivated by an acid pH.<sup>[107]</sup> It can be combined with halobetasol ointment or cream or with 5% tar gel, however, it is degraded when mixed with 6% salicylic acid, 12% ammonium lactate or hydrocortisone-17 valerate ointment.<sup>[108]</sup>

#### Topical Vitamin D analog use in pregnancy and pediatric population

Treatment with Vitamin D analogs during pregnancy is rated Category C.<sup>[65]</sup> Vitamin D analogs have not been

found to be teratogenic in animals, although no clinical data on humans has been reported. The use of calcipotriene for the treatment of psoriasis in children is effective, and the dose should not exceed 50 g/week.<sup>[109]</sup>

### Newer Vitamin D analogs

Newer Vitamin D analogs including maxacalcitol, paricalcitol, and becocalcidiol are being studied for the treatment of psoriasis. They appear to be promising drugs for the treatment of plaque psoriasis.<sup>[110-112]</sup>

### Conclusion

Topical therapies are the backbone of management of psoriasis. They are safe and well tolerated by the patients. TCS and Vitamin D analogs are the treatment of choice among the various topical agents available for psoriasis. TCI can be used as steroid-sparing agents on the face and intertriginous areas. Tazarotene can be used as an effective maintenance therapy.

New vehicle formulations such as gels, lotions, solutions, shampoos, foams, etc., have been developed to improve the aesthetics, and thereby the patient compliance which is of utmost importance for optimum results.

New insights in the pathogenesis of psoriasis have enabled identification of new therapeutic targets. Target-based topical agents are being developed and tested. Moreover, advancement in nanotechnology has led to the possibility of improving the efficacy of topical agents and minimizing their side effects. The advent of newer molecules and newer drug delivery systems will significantly expand the therapeutic armamentarium for the treatment of psoriasis.

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### Conflicts of interest

There are no conflicts of interest.

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