

Psoriasis Agents, Topical Review

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Psoriasis Agents, Topical Review

FDA-Approved Indications

Drug	Manufacturer	FDA-Approved Indications	
		Plaque psoriasis (psoriasis vulgaris)	Psoriasis of scalp
anthralin (Psoriatec™) ¹	generic Sirius Labs	X*	X
calcipotriene cream (Dovonex®) ²	Warner Chilcott	X	--
calcipotriene (Dovonex® Scalp solution) ³	generic	--	X
calcipotriene/ betamethasone ointment (Taclonex®) ⁴	Warner Chilcott	X	--
calcipotriene/ betamethasone topical suspension (Taclonex Scalp®) ⁵	Warner Chilcott	--	X
calcitriol (Vectical™) ⁶	Galderma	X	--
tazarotene (Tazorac®) ^{7,8}	Allergan	X	--

*Anthralin is FDA-approved for quiescent or chronic psoriasis.

Calcipotriene (Dovonex) scalp solution and calcipotriene/betamethasone (Taclonex Scalp) topical suspension are approved for the treatment of moderate to severe psoriasis of the scalp.

Calcipotriene/betamethasone (Taclonex) ointment is indicated for use up to four weeks. Calcipotriene/betamethasone (Taclonex Scalp) topical suspension is indicated for two weeks or until clear and if needed treatment may be continued for up to a maximum of eight weeks. Neither formulation is recommended for treatment of greater than 30 percent of BSA.

Calcitriol (Vectical) is indicated for the topical treatment of mild to moderate plaque psoriasis in adults 18 years and older.

Tazarotene (Tazorac) gel is indicated for stable plaque psoriasis of up to 20 percent body surface area (BSA) involvement. Tazarotene (Tazorac) 0.1% cream and 0.1% gel are also indicated in facial acne vulgaris.

Overview

Psoriasis is a chronic, auto-immune disease that appears on the skin. It is estimated that psoriasis affects approximately 7.5 million people in the US.⁹ The prevalence of psoriasis is 1.3 percent in African Americans versus 2.5 percent in Caucasians.¹⁰ It usually presents between the ages of 15 to 25 years, but psoriasis can develop at any age. There are five types of psoriasis: plaque, guttate, inverse, pustular, and erythrodermic. The most common type is plaque psoriasis (psoriasis vulgaris) in which patches or “lesions” of skin become inflamed and are covered by a silvery white scale. The plaques frequently occur on the skin of the elbows and knees but can affect any area including the scalp. Psoriasis can range from mild, moderate to severe disease. Psoriasis can be associated with comorbidities including cardiovascular disease, type 2 diabetes mellitus, metabolic syndrome, cancer, and depression.^{11,12,13,14,15}

Although not completely understood, there is hyperproliferation and abnormal differentiation of the psoriatic epidermis.¹⁶ The delay in the expression and an over-expression of keratins mark the abnormal differentiation. Inflammatory cell infiltrates and vascular changes are part of the pathophysiology.¹⁷

Psoriasis can also affect the joints and connective tissue. Psoriatic arthritis affects up to 30 percent of people with psoriasis.¹⁸ The management of psoriatic arthritis will not be reviewed in this document. Instead, this review will focus on topical treatment of plaque and scalp psoriasis.

Traditionally, pharmacotherapy choices include emollients, topical corticosteroids, phototherapy, and systemic medications.¹⁹ The 2009 evidence-based clinical practice guidelines developed by the American Academy of Dermatology (AAD), indicate that approximately 80 percent of patients affected with psoriasis have mild to moderate disease that can be managed with topical agents.²⁰ Topical corticosteroids are the cornerstone of treatment for most patients with psoriasis, especially for those with limited disease, and the wide availability of strengths and formulations favorably allow for versatility of use. Limitations do exist though with topical steroid use. The clinical data available for the safety and efficacy of topical corticosteroids has a short duration of approximately two to four weeks, which continued treatment extending beyond increases the risk of cutaneous adverse effects and systemic absorption. Also, rebound exacerbation of the disease has been reported with abrupt discontinuation of the corticosteroid, so tapering is recommended, but guidelines do not exist on the details of tapering. Both systemic and local cutaneous adverse effects are a concern with extensive use of corticosteroids, such as telangiectasia, striae distensae, acne, folliculitis, and purpura. As a result, despite the corticosteroids being the mainstay of topical treatment of psoriasis, the most potent and efficacious of these agents are approved for short-term treatment for about two to four weeks. Furthermore, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) advise that the use of topical steroids helps to improve the symptoms of the disease, such as itching, but do not eliminate the disease.²¹ Often times the affected skin will become resistant to the topical steroid and other treatments will have to be used instead; therefore, other topical agents have been developed, which have demonstrated efficacy and will be the focus of this review. These topical agents include anthralin, tazarotene (Tazorac) - a retinoid, calcitriol (Vectical) - a vitamin D₃ analog, calcipotriene (Dovonex) - a vitamin D₃ analog, and calcipotriene/betamethasone (Taclonex, Taclonex Scalp) - a combination product of the vitamin D₃ analog and a corticosteroid. Phototherapy is reserved for widespread disease, or

when the psoriasis is unresponsive to topical treatment. Systemic therapies are reserved for moderate to severe disease. Therapies for psoriasis are not curative but rather symptomatic management.²²

Pharmacology^{23,24,25,26,27,28,29,30,31,32,33}

Though the agents have different mechanisms of action, they have an effect to normalize skin cell production and reduce inflammation.

The exact mechanism of action of anthralin is unknown, but it is believed to have both anti-proliferative and anti-inflammatory properties. Anthralin acts by reducing the mitotic rate and proliferation of epidermal cells in psoriasis by inhibiting synthesis of nucleic protein from inhibition of DNA synthesis. It has been shown to inactivate 12-lipoxygenase and reduce the levels of endothelial adhesion molecules, and as a result the inflammatory metabolites that are produced from this enzyme are theoretically reduced in the psoriatic plaques. Recent studies suggest that it has a direct effect on mitochondria, which then prevents T-lymphocyte activation and normalizes keratinocyte differentiation.

Tazarotene (Tazorac) is a synthetic, acetylenic retinoid, which modulates differentiation and proliferation of epithelial tissue and exerts some degree of anti-inflammatory and immunological activity.

Calcitriol (Vectical) is a vitamin D₃ analog, but the mechanism of action in the treatment of psoriasis has not been established.

Calcipotriene (Dovonex) is a synthetic vitamin D₃ analog which is believed to regulate skin cell production and proliferation.

Taclonex is a combination of the vitamin D₃ analog, calcipotriene, and a high potency corticosteroid, betamethasone dipropionate. Like other corticosteroids, betamethasone has anti-inflammatory, antipruritic, and vasoconstrictive properties.

Pharmacokinetics^{34,35,36,37,38,39,40,41}

Due to the nature of topical application, all products are minimally exposed to the systemic circulation.

Ointment: The vehicle is oil based and has been theorized to be the most effective vehicle for psoriasis due to its occlusive nature and moisturizing ability. No proof of the ointment's superior effectiveness as a vehicle is available, and preference of the ointment is typically low since it is greasier and messier than other available vehicle choices.⁴²

Cream: These are oil-in-water emulsions. Creams tend to be less greasy than ointments and may be more appealing cosmetically.

Gel: These 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.

Solution: These are water based and can have a drying effect. Solutions are easier to apply to larger areas such as the scalp.

Systemic absorption of anthralin cream after topical administration has not been determined in humans.

The systemic absorption of calcipotriene (Dovonex) cream has not been studied; the calcipotriene solution is less than one percent systemically absorbed. Calcipotriene is rapidly metabolized in the liver to primary metabolites less potent than the parent compound.

Calcipotriene (Taclonex, Taclonex Scalp) is rapidly metabolized in the liver to primary metabolites less potent than the parent compound.

Calcitriol (Vectical) ointment is absorbed through the skin and metabolized in the liver to hydroxy metabolites, it is further metabolized via hydroxylation in the kidney. Calcitriol and its metabolites are primarily excreted via the bile with some renal elimination.

Tazarotene (Tazorac) cream or gels have minimal absorption following cutaneous application. The pro-drug is rapidly metabolized by esterases to an active metabolite, tazarotenic acid.

Corticosteroids are metabolized primarily in the liver and excreted by the kidneys.

Contraindications/Warnings^{43,44,45,46,47,48,49,50,51}

Hypersensitivity to these agents and any of their components is considered a contraindication. These agents are for external use only and should only be applied to affected areas; avoid contact with eyes and mucous membranes. Transient irritation of both lesions and surrounding uninvolved skin may occur.

Tazarotene (Tazorac) is contraindicated in women who are or may become pregnant. Tazarotene may cause photosensitivity; exposure to sunlight should be avoided (use sunscreen/wear protective clothing), and tazarotene should not be used on sunburned skin. Photosensitivity risk can be increased with concurrent therapy with known photosensitizers (thiazides, tetracyclines, fluoroquinolones, phenothiazines, or sulfonamides). Tazarotene should not be applied to eczematous skin as it can cause severe irritation. Avoid application over extensive areas.

Anthralin is contraindicated in acute psoriasis or actively inflamed psoriatic eruptions. Anthralin can cause temporary discoloration of skin, hair and fingernails and permanent staining of fabrics, but it can be minimized by careful application. Anthralin should be used with caution in renal impairment.

Calcitriol (Vectical) and products containing calcipotriene should not be used in patients with known or suspected disorders of calcium metabolism or hypercalcemia or evidence of vitamin D toxicity. Additionally, none of these products should be used in patients with erythrodermic, exfoliative, or pustular psoriasis. Calcitriol and calcipotriene containing products should not be used on the face, and calcitriol should not be applied to the eyes or lips. Photosensitivity can occur with all of these products so excessive exposure to natural or artificial sunlight should be avoided. Also, use of phototherapy in these patients should be avoided while using calcitriol or calcipotriene due to the increased risk of skin tumors, which was demonstrated in preclinical trials in mice. Calcipotriene/betamethasone ointment and topical suspension are not recommended for application to the face, axillae, or groin. Calcipotriene scalp solution is flammable and should be kept away from open flames.

Drug Interactions^{52,53,54,55,56,57,58,59}

Based on the minimal extent of systemic absorption with these agents, interactions with systemically administered drugs are unlikely to occur.

Concomitant dermatologic medication and cosmetics that have a strong drying effect should be avoided.

Calcipotriene (Dovonex) is inactivated by acid pH so may not be stable when applied with some other topical products.⁶⁰

Calcitriol (Vectical) is a vitamin D₃ analog and has the potential to increase serum calcium levels. Patients receiving medications that may increase serum calcium levels such as thiazide diuretics, calcium supplements, and high dose vitamin D supplements should be closely monitored.⁶¹

Long-term use of topical corticosteroids may destabilize psoriasis and withdrawal may also give rise to a “rebound” phenomenon. Allow an interval of at least one week between the discontinuance of topical corticosteroids and the commencement of anthralin therapy.

Tazarotene (Tazorac) can interact with known photosensitizers such as thiazides, tetracyclines, fluoroquinolones, phenothiazines, or sulfonamides.

Adverse Effects^{62,63,64,65,66,67,68,69,70}

Drug	Skin Burning	Pruritus	Skin Erythema	Rash	Skin Irritation
anthralin (Psoriatec)	nr	nr	nr	nr	Reported
calcipotriene (Dovonex)	23 (solution)	1-10 (cream)	nr	1-10 (cream) 11 (solution)	10-15 (cream) 1-5 (solution)
calcitriol (Vectical)	reported	1-3	reported	nr	3
calcipotriene/betamethasone (Taclonex, Taclonex Scalp)	0.2 (ointment) 1 (suspension)	3.1 (ointment) 6.3 (suspension)	0.6 (ointment) 2.1 (suspension)	1.2 (ointment) <1 (suspension)	0.4 (ointment) 1.4 (suspension)
tazarotene (Tazorac)	10-23 (cream) 10-30 (gel)	10-23 (cream) 10-30 (gel)	10-23 (cream) 10-30 (gel)	<10 (cream) 1-10 (gel)	~ 10 (cream & gel) 10-30 (gel)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. nr = not reported.

Anthralin causes temporary discoloration of skin, hair and fingernails and permanent staining of fabrics.

Calcipotriene (Dovonex), calcipotriene/betamethasone (Taclonex, Taclonex Scalp), and calcitriol (Vectical) can cause hypercalcemia. The manufacturer doesn't recommend use of the combination product (Taclonex) for longer than four weeks due to the risk of systemic corticosteroid adverse effects.

Tazarotene (Tazorac) 0.1% cream has greater local irritation than tazarotene 0.05% cream. Tazarotene causes peri-lesional irritation.

In large doses and applied over a prolonged length of time, corticosteroids can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression.⁷¹

Special Populations^{72,73,74,75,76,77,78,79,80}

Pediatrics

Due to a higher ratio of skin surface area to body mass, pediatric patients are at greater risk than adults for systemic adverse effects when they are treated with topical medication.

For use in psoriasis, the safety and efficacy of these agents have not been established in pediatric patients under the age of 18 years and under the age of 12 years for tazarotene (Tazorac) gel.

Pregnancy

These agents are Pregnancy Category C with the exception of tazarotene which is Pregnancy Category X.

Geriatrics

These agents have limited data on the safety and efficacy of use in patients greater than 65 years of age. Calcitriol (Vectical) indicated that reported use of the drug in this population has not identified differences in response between elderly and young patients. The clinical studies for calcipotriene (Dovonex cream and scalp solution) and calcipotriene/betamethasone (Taclonex ointment and topical suspension) had less than 20 percent of patients greater than 65 years of age and documented no differences in adverse events compared to patients younger than 65 years of age, but each manufacturer warned of the potential for greater sensitivity to these agents in the geriatric population. Similarly, tazarotene cream (Tazorac cream) had not demonstrated any significant differences in efficacy or safety during clinical studies between patients less than 65 years of age and greater than 65 years of age; however, tazarotene gel (Tazorac 0.05% and 0.1% gel) did demonstrate that patients greater than 65 years of age did experience more adverse events and had lower success rates than patients younger than 65 years of age after 12 weeks of use. All manufacturers indicate that the potential for greater sensitivity can not be ignored, and studies demonstrating the safety of these products in patients greater than 65 years of age have not been performed or are limited.

Dosages^{81,82,83,84,85,86,87,88,89}

Drug	Adult	Children ≥ 12 years	Availability
anthralin (Psoriatec)	Apply sparingly to lesions once daily or as directed, and remove after specified time as directed.	--	Psoriatec 1% cream - 50 gm -
calcipotriene (Dovonex)	Apply twice daily for eight weeks.	--	0.005% cream- 60, 120 gm 0.005% solution - 60 mL bottle
calcitriol (Vectical)	Apply to the affected areas twice daily. Maximum weekly dose should not exceed 200 grams.	--	3 mcg/gm ointment - 5, 100 gm
tazarotene (Tazorac)	Apply once daily.	Apply tazarotene gel once daily	0.05% & 0.1% cream - 30, 60 gm 0.05% & 0.1% gel - 30, 100 gm
calcipotriene/ betamethasone (Taclonex, Taclonex Scalp)	Apply once daily for up to four weeks.	--	Calcipotriene/betamethasone 0.005%/0.064% ointment - 60, 100 gm Calcipotriene/betamethasone 0.005%/0.064% topical suspension - 15, 30, 60, 2 x 60 gm

Clinical Trials

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled trials studying agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated

for validity and importance.

Numerous clinical trials were found using these search methods. Other trials not appearing here were excluded based on the potential for bias, such as the absence of double-blinding, or the inclusion of too few patients for the study to be deemed clinically relevant. Comparative data within this class are lacking. Calcipotriene is the chemical name used in the US, and calcipotriol is the chemical name used in Canada and Europe; therefore, calcipotriol studies have been included.⁹⁰

The Psoriasis Area Severity Index (PASI) is the most widely used measurement tool for psoriasis and assesses the severity of lesions and the area affected. After PASI, Physicians' Global Assessment (PGA) is the most common tool used to measure psoriasis severity.⁹¹

calcipotriol/betamethasone versus calcipotriol versus betamethasone

A randomized, double-blind, parallel-group, multicenter, eight week study compared the efficacy of the combination of calcipotriol and betamethasone dipropionate versus the individual components.⁹² Patients with scalp psoriasis involving greater than 10 percent of the scalp were randomized to receive either the combination product calcipotriol 0.005%/betamethasone dipropionate 0.05% (n=568), calcipotriol 0.005% (n=286), or betamethasone dipropionate 0.05% (n=563). The primary outcome measure was to determine the proportion of patients achieving 'absence of disease' or 'very mild disease' per investigators' assessments at week eight. The primary outcome was determined to be significantly greater in the combination product group (68.4 percent) versus either single agent group [61 percent of the betamethasone dipropionate group (p=0.0079) and 43.4 percent of the calcipotriol group (p<0.0001)]. In addition, patients' self-assessment of whether the scalp psoriasis was 'clear' or 'almost clear' at eight weeks was significantly higher in the combination product group (69.6 percent) versus either single agent group [59.9 percent of the betamethasone dipropionate group (p=0.0006) and 44.7 percent of the calcipotriol group (p<0.0001)].

A randomized, double-blinded study of 634 patients with psoriasis compared 52 weeks of calcipotriol/betamethasone, 52 weeks of alternating four week periods of calcipotriol/betamethasone and calcipotriol (alternating group), or four weeks of calcipotriene/betamethasone followed by 48 weeks of calcipotriol (calcipotriol group).^{93,94} All treatments were applied once daily and only when needed. There was a trend towards a difference between treatments from the overall treatment effect for the percentage of satisfactory responses for each patient during the study (p=0.071). This appeared to be due to the comparison of the calcipotriol/betamethasone group and calcipotriol groups (p=0.025); therefore, a trend towards the efficacy of the calcipotriol/betamethasone group being better than the alternating group followed by the calcipotriol group was observed. Adverse reactions occurred in 21.7 percent, 29.6 percent, and 37.9 percent of the calcipotriol/betamethasone, alternating, and calcipotriol groups, respectively. The odds ratio for an adverse event in the calcipotriol/betamethasone group was 0.46 (95 percent confidence interval, 0.30-0.70, p<0.001).

calcipotriol/betamethasone (Taclonex Scalp) versus calcipotriol

An international, double-blind, randomized study investigated the efficacy and safety in 869 patients with moderate to severe scalp psoriasis for 52 weeks.⁹⁵ Patients were randomized to either a two-compound scalp formulation of calcipotriol 50 mcg/g plus betamethasone dipropionate 0.5 mg/g (n=429) or calcipotriol (n=440). Results demonstrated that adverse events were less frequent in the two-compound group compared with the calcipotriol group

(17.2 percent versus 29.5 percent; $p < 0.001$). Incidences of adverse events possibly associated with long-term corticosteroid use were low in both the two-compound (2.6 percent) and the calcipotriol (three percent) groups. Disease was satisfactorily controlled in 92.3 percent of visits in the two-compound group versus 80 percent in the calcipotriol group ($p < 0.001$).

calcipotriol versus betamethasone

A randomized, double-blind, parallel-group, multicenter study compared the safety and efficacy of calcipotriol cream 50 mcg/gm versus betamethasone 1 mg/gm in 421 patients with mild to moderate plaque psoriasis.⁹⁶ After a two week washout, treatments were applied twice daily for eight weeks or until complete clearing had occurred. The mean percentage reduction in PASI from baseline to end of treatment was 47.8 percent in calcipotriol group and 45.4 percent in the betamethasone group. The difference between groups was not statistically significant. Both investigators' and patients' overall assessment of treatment response at study end showed no difference between groups. Adverse events in the calcipotriol group were reported more frequently than in the betamethasone group. Lesional and perilesional irritation was reported in 16 percent and nine percent ($p = 0.03$), and facial irritation in 10 percent and 0.5 percent ($p < 0.001$), when comparing the calcipotriol group to the betamethasone group.

calcipotriene/betamethasone (Taclonex) versus calcipotriene (Dovonex) versus betamethasone

Six randomized, double-blinded, Phase III studies of 6,050 patients with psoriasis evaluated the efficacy and tolerability of calcipotriol and betamethasone ointment compared to monotherapy with each component.⁹⁷ After four weeks of treatment, the PASI ranged from 65 to 74 percent for the combination product applied once or twice daily, from 46 to 59 percent for calcipotriol, and from 57 to 63 percent for betamethasone. Tolerability of the combination product was similar to betamethasone monotherapy and better than calcipotriol alone.

A prospective, randomized, double-blind, parallel-group, multicenter, four week study compared the efficacy of a fixed combination of calcipotriene and betamethasone to calcipotriene, betamethasone, and vehicle in 1,028 patients with plaque psoriasis.⁹⁸ The mean percentage of reduction in PASI from baseline to end of treatment was 73.2 percent, 48.8 percent, 63.1 percent, and 28.8 percent, in the combination, calcipotriene, betamethasone, and vehicle, respectively ($p < 0.001$). The mean reduction during the first week was 48.1 percent, 28.4 percent, 41.4 percent, and 21.5 percent, respectively ($p < 0.001$).

A randomized, double-blind study of 1,603 patients with psoriasis compared the combination ointment of calcipotriene 50 mcg/gm and betamethasone 0.64 mg/gm to monotherapy with the individual components and vehicle, each applied once daily for four weeks.⁹⁹ The mean decrease in PASI score from baseline to study end was 73.1 percent, 57.2 percent, 46.1 percent, and 22.7 percent with the combination, betamethasone, calcipotriene, and vehicle, respectively.

A parallel-group study of 1,136 patients with plaque psoriasis, randomized patients to one of the three treatment groups: four weeks of calcipotriene/betamethasone followed by eight weeks of calcipotriene cream (the calcipotriene group), four weeks of calcipotriene daily followed by eight weeks on weekdays and calcipotriene/betamethasone on weekends (the alternating group), and four weeks of calcipotriene/betamethasone followed by eight weeks of vehicle (the vehicle group).¹⁰⁰ All were applied once daily. The first four weeks of treatment were not double-blinded. The following eight weeks of therapy with calcipotriene and vehicle were completed in a double-blind manner; however, the identity of the cream and ointment could be ascertained. The mean

percentage reduction in PASI from baseline to study end was 44.5 percent, 58.4 percent, and 33.1 percent in the calcipotriene, alternating, and vehicle groups, respectively (p<0.001).

calcipotriene/betamethasone (Taclonex Scalp) versus calcipotriene versus betamethasone

An eight week, multicenter, randomized, double-blind study compared the efficacy and safety of a once-daily, two compound scalp formulation containing calcipotriene plus betamethasone dipropionate with the individual components in the same vehicle and the vehicle alone.¹⁰¹ Patients with scalp psoriasis were randomized to treatment with the two-compound scalp formulation (calcipotriene 50 mcg/g plus betamethasone dipropionate 0.5 mg/g) (n=541), betamethasone dipropionate 0.5 mg/g in the same vehicle (n=556), calcipotriene 50 microg/g in the same vehicle (n=272), or vehicle alone (n=136). Results demonstrated that more patients achieved "absent" or "very mild" disease at week eight with the two-compound scalp formulation (71.2 percent) compared with betamethasone dipropionate in the same vehicle (64 percent, p=0.011), calcipotriene in the same vehicle (36.8 percent, p<0.0001), or the vehicle (22.8 percent, p<0.0001). One of the study limitations was that efficacy of the active comparators in the study has not been established in relation to calcipotriene and betamethasone formulations available for clinical use.

Two randomized, double-blinded, multicenter studies with 1,407 and 1,280 patients with moderate to severe scalp psoriasis assessed the efficacy of calcipotriene/betamethasone topical suspension versus betamethasone dipropionate in the same vehicle, and calcipotriene hydrate in the same vehicle.¹⁰² Study one also included a vehicle alone arm and 494 patients received calcipotriene/betamethasone, 531 patients received betamethasone dipropionate, 256 patients received calcipotriene, and 126 patients received vehicle alone. In study two 512 patients received calcipotriene/betamethasone, 517 patients received betamethasone dipropionate, and 251 patients received calcipotriene. Treatment was given once daily for eight weeks in both studies. Efficacy was assessed using an Investigator's Global Assessment of Disease Severity, with "clear" defined as no evidence of redness, thickness, or scaling and "almost clear" as an overall clinical picture of lesions with the presence of minimal erythema. In study one and two respectively, 70 and 67.2 percent, 63.1 and 59.6 percent, and 36.7 and 41 percent of patients in the calcipotriene/betamethasone topical suspension, betamethasone dipropionate alone, and calcipotriene alone were clear or almost clear according to the Investigator's Global Assessment of Disease Severity.

calcipotriol versus calcitriol (Vectical)

A randomized, multicenter, investigator-masked, and parallel comparison study evaluated the safety and efficacy of calcitriol 3 mcg/gm versus calcipotriol 50 mcg/gm applied twice daily for 12 weeks in patients with mild to moderate chronic plaque-type psoriasis.¹⁰³ Efficacy was evaluated based on global improvement scale (a 4-point scale from 0: no change or worse, to 3: clear or almost clear) assessed by the investigator and by the subject. Also, the dermatological sum score (sum of the scores for erythema, plaque elevation, and scaling) was evaluated at each study visit. Safety evaluations included adverse event reporting, cutaneous safety assessed by the investigator, and cutaneous discomfort assessment by the subject (both on a 5-point scale from 0: none, to 4: very severe). A total of 250 subjects of both genders were recruited. At week 12, the mean score of global improvement rated by the investigator was similar between both groups, 2.27 for calcitriol versus 2.22 for calcipotriol. The mean score of global improvement was rated by the patient and was similar between both agents, 2.12 for calcitriol versus 2.09 for calcipotriol. A greater percentage of patients with at least marked improvement was reported in the calcitriol group versus the calcipotriol group (95.7 percent versus 85 percent, respectively), but the difference was not statistically significant. The mean

worst score for the cutaneous safety assessment was higher in the calcipotriol versus the calcitriol group (0.3 versus 0.1 as rated by the investigator and 0.4 versus 0.2 as rated by the patient, respectively). Calcitriol had a statistically significant better safety profile than calcipotriol ($p=0.0035$). Fourteen dermatological and treatment-related adverse events were reported with calcipotriol versus only five with calcitriol.

calcitriol (Vectical)

Two multicenter, randomized, vehicle-controlled, double-blind, parallel group studies evaluated the efficacy and safety of calcitriol in the treatment of mild to moderate chronic plaque psoriasis.¹⁰⁴ Patients were randomized to either calcitriol 3 mcg/gm or vehicle applied twice a day for eight weeks. Efficacy was evaluated through a Global Severity Score dichotomized in success (clear or minimal) or failure. Efficacy was also assessed via global improvement, erythema, pruritus, plaque elevation, scaling, and dermatologic sum score (sum of the scores for erythema, plaque elevation, and scaling). Safety parameters and clinical lab values were monitored throughout the study, including calcium homeostasis. A total of 839 subjects were included in the two studies, 419 patients were randomized to receive calcitriol 3 mcg/gm ointment and 420 the vehicle twice a day. In both studies, calcitriol 3 mcg/gm ointment demonstrated that it was more effective than its vehicle, with onset of therapeutic effect seen as early as week two and sustained at all subsequent visits. Calcitriol 3 mcg/gm ointment demonstrated good systemic and local safety profile comparable to its vehicle with no effect on calcium homeostasis.

tazarotene (Tazorac)

Two randomized, double-blind, multicenter, vehicle-controlled trials assessed the safety and efficacy of once daily tazarotene creams 0.05% and 0.1% for 12 weeks in the treatment of 1,303 patients with psoriasis.¹⁰⁵ Both strengths showed reductions in the severity of the clinical signs of psoriasis at 12 weeks, and the therapeutic effect was maintained during a 12 week post treatment period. Tazarotene 0.1% cream was generally more effective though slightly less well tolerated than tazarotene 0.05%. The incidence of local skin irritation was 8.6, 7.3, and 0.4 percent in the tazarotene 0.1%, 0.05%, and vehicle, respectively, in the first study. In the second study, the incidence of local skin irritation was 10, 7.1, and 2.8 percent in the tazarotene 0.1%, 0.05%, and vehicle, respectively. The among-group p -values for both groups in both studies were $p \leq 0.05$.

A randomized, double-blind, parallel-group, multicenter study of 324 patients with stable plaque psoriasis compared once daily tazarotene gel 0.1%, 0.05%, and vehicle over 12 weeks.¹⁰⁶ Both strengths were more efficacious than vehicle as early as the first week in all efficacy measures [plaque elevation, scaling and erythema ($p < 0.05$)]. The therapeutic effect was maintained during the 12 week post treatment period. The incidence of pruritus was 23, 17, and 8 percent in the tazarotene 0.1%, 0.05%, and vehicle groups, respectively. The incidence of burning was (19, 15, and 6 percent) and the incidence of erythema (8, 7, and 1 percent), respectively.

Meta-analyses

A systematic review of 37 randomized controlled trials of 6,038 patients with mild to moderate chronic plaque psoriasis, showed that calcipotriol was at least as effective as potent topical corticosteroids, calcitriol, short contact dithranol, tacalcitol, coal tar and combined coal tar 5%, allantoin 2%, and hydrocortisone 0.5%. At eight weeks, only potent corticosteroids appeared to have comparable efficacy. The primary adverse event of calcipotriol was skin irritation.¹⁰⁷

A systematic review of 41 randomized placebo (vehicle) controlled trials of 3,380 patients and 28 randomized comparative studies of 4,898 assessed the effectiveness and tolerability of topical therapies in patients with psoriasis.¹⁰⁸ Clinical outcomes were pooled using a random effect standardized weighed mean difference (SWMD) metric. The results were strongly in favor of active treatments versus vehicle, SWMD -1.06 (95% CI, -1.26 to -0.86), approximately a two point improvement on a 12-point Total Severity Score (TSS). The only significantly different benefit was for very potent corticosteroids, SWMD -1.51 (95% CI, -1.76 to -1.25), approximately a three point improvement on a 12-point TSS. The comparative studies had similar results with one exception: calcipotriol was more effective than dithranol, coal tar, and other vitamin D₃ derivatives. Combination therapy with calcipotriol and a potent steroid was more effective than calcipotriol monotherapy. No major differences in adverse events or withdrawal rates were identified.

A Cochrane database systematic review compared the effectiveness, tolerability, and safety of topical treatments for chronic plaque psoriasis with placebo and vitamin D analogues with other topical treatments, in 131 randomized controlled trials with 21,448 patients.¹⁰⁹ Compared to placebo, vitamin D analogues were significantly more effective, although there was a wide variation in effect size with the standardized mean difference (SMD) ranging from -0.82 (95% CI, -1.34 to -0.29) to -1.90 (95% CI, -2.09 to -1.71). All but one of the corticosteroids performed better than placebo. Dithranol and tazarotene performed better than placebo. There were no significant differences when vitamin D analogues were compared to potent or very potent corticosteroids. However, combination therapy with vitamin D/corticosteroid performed significantly better than either vitamin D or corticosteroid monotherapy. Vitamin D performed better than coal tar, but there was conflicting information on dithranol. Potent corticosteroids were less likely than vitamin D analogues to cause local adverse events. There were no significant differences in systemic adverse events for the topical therapies.

Summary

A variety of topical agents are available for the treatment of psoriasis, but valid comparative trials of many of these agents are lacking. Per the 2009 AAD psoriasis guidelines, 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. Furthermore, psoriasis can become resistant to corticosteroid treatment. 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 the guidelines recommend limiting the use of the topical medications to patients with mild to moderate psoriasis and the systemic agents to severe disease.

Anthralin is one of the oldest, least tolerable topical psoriasis agents available and is only indicated in chronic psoriasis. Patient compliance is a major issue with anthralin since it can cause temporary discoloration of skin, hair, and fingernails and permanent staining of fabrics and bathroom fixtures.

Calcipotriene (Dovonex), a vitamin D analog, 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 (Taclonex, Taclonex Scalp). Calcitriol (Vectical), another vitamin D analog, is indicated for the topical treatment of mild to moderate plaque psoriasis. Tazarotene (Tazorac)

can be used as monotherapy or predominantly in combination therapy. Tazarotene (Tazorac) should be used with caution in patients who are pregnant or planning pregnancy due to its teratogenic potential.

Currently, few studies compare the various treatments available, so guidelines are not currently available to support the use of one drug over another drug. The various treatment modalities have advantages and disadvantages; selection of a topical agent should take into account disease severity, location, tolerability, and clinical response.

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