Guidelines of care for the management of psoriasis and psoriatic arthritis

Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies

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Psoriasis is a common, chronic, inflammatory, multi-system disease with predominantly skin and joint manifestations affecting approximately 2% of the population. In this third of 6 sections of the guidelines of care for psoriasis, we discuss the use of topical medications for the treatment of psoriasis. The majority of patients with psoriasis have limited disease (<5% body surface area involvement) and can be treated with topical agents, which generally provide a high efficacy-to-safety ratio. Topical agents may also be used adjunctively for patients with more extensive psoriasis undergoing therapy with either ultraviolet light, systemic or biologic medications. However, the use of topical agents as monotherapy in the setting of extensive disease or in the setting of limited, but recalcitrant, disease is not routinely recommended. Treatment should be tailored to meet individual patients' needs. We will discuss the efficacy and safety of as well as offer recommendations for the use of topical corticosteroids, vitamin D analogues, tazarotene, tacrolimus, pimecrolimus, emollients, salicylic acid, anthralin, coal tar, as well as combination therapy. (J Am Acad Dermatol 2009;60:643-59.)

DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient.

Abbreviations used:

AAD: American Academy of Dermatology
HPA: hypothalamic-pituitary-adrenal (axis)
PASI: Psoriasis Area and Severity Index
PGA: physician's global assessment

SCOPE

This third section covers the management and treatment of psoriasis with topical therapies.

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METHOD

A work group of recognized psoriasis experts was convened to determine the audience for and scope of the guideline and to identify clinical questions to structure the primary issues in diagnosis and management discussed in American Academy of Dermatology (AAD) psoriasis guidelines Sections 1 and 2.[1,2] Work group members completed a disclosure of commercial support.

An evidence-based model was used and evidence was obtained using a search of the MEDLINE database spanning the years 1960 through 2008.

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy developed by editors of the US family medicine and primary care journals (ie, *American Family Physician*, *Family Medicine*, *Journal of Family Practice*, and *BMJ USA*). This strategy was supported by a decision of the Clinical Guidelines Task Force in 2005 with some minor modifications for a consistent approach to rating the strength of the evidence of scientific studies.[3] Evidence was graded using a 3-point scale based on the quality of methodology as follows:

I. Good-quality patient-oriented evidence
II. Limited-quality patient-oriented evidence
III. Other evidence including consensus guidelines, opinion, or case studies

Clinical recommendations were developed on the best available evidence tabled in the guideline. These are ranked as follows:

A. Recommendation based on consistent and good-quality patient-oriented evidence
B. Recommendation based on inconsistent or limited-quality patient-oriented evidence
C. Recommendation based on consensus, opinion, or case studies

In those situations where documented evidence-based data are not available, we have utilized expert opinion to generate our clinical recommendations. Prior guidelines on psoriasis were also evaluated.[4,5] This guideline has been developed in accordance with the AAD/AAD Association "Administrative Regulations for Evidence-based Clinical Practice Guidelines," which include the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors.

GENERAL PRINCIPLES

Approximately 80% of patients affected with psoriasis have mild to moderate disease. The majority of these patients can be treated with topical agents which generally provide both high efficacy and safety. Topical agents are also used adjunctively for resistant lesions in patients with more extensive psoriasis who are being concurrently treated with either ultraviolet light or systemic medications. However, the use of topical agents as monotherapy in the setting of extensive disease or in the setting of limited, but recalcitrant disease is not routinely recommended. Treatment should be tailored to meet individual patients' needs. These needs vary depending on body location, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences. It is important to match patient expectations with practical considerations. Patients who wish for lifetime clearance with no evident lesions will inevitably be disappointed with topical therapy because of the need for a continuous intense topical regimen that will be very difficult to carry out and maintain. Some patients may desire to be free from pruritus and to have a diminution in their most visible lesions. Others may prefer only intermittent treatment with little interest in spending considerable time to care for their psoriasis. It is important to ascertain each patient's goals and then to develop a strategy to help fulfill his or her expectations while also being practical and realistic.

The choice of vehicle can significantly alter the use and penetration of the medication and therefore alter the efficacy. Vehicle types are numerous and may include ointments, creams, solutions, gels, foams, tape, sprays, shampoos, oils, and lotions. Different vehicles are indicated for different body sites. The optimal choice is generally the vehicle the individual patient will most likely use. For example, hair-bearing areas including the scalp can be treated with solutions, foams, shampoos, sprays, oils, gels, or other vehicles, with individual patients having different preferences among these options. Some patients may prefer a less greasy preparation, perhaps a cream for daytime use and may be willing to use an ointment, which is more effective but less cosmetically appealing, at night. Cultural preferences may also make one vehicle preferred over others for a given site. Occlusion of topical medications can also alter the penetration, thereby varying the effectiveness. The observation that flurandrenolide 0.1%, which is a class 5 topical steroid when used in the cream or lotion formulation, functions as a class 1 topical steroid when used as a tape and has a higher efficacy than the class 1 steroid diflorasone diacetate ointment in the treatment of psoriasis[6] serves as a strong reminder of the impact of occlusion.

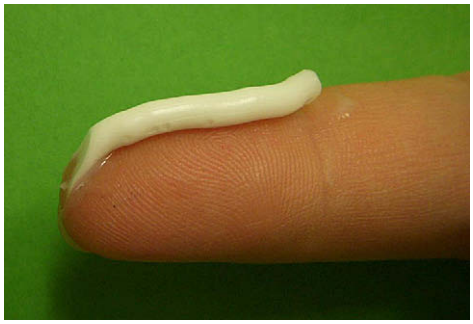

Fig 1. Use of topical agents—the fingertip unit and how to assess quantity of topical agents needed to cover a given body surface area. One fingertip unit is approximately 500 mg.[79]

Topical medications can sometimes be used concurrently to take advantage of varied mechanisms of action. For example, calcipotriene can be used in combination with topical corticosteroids. However, when using multiple topical agents, it is important to be aware of possible compatibility issues. For example, calcipotriene should not be used concurrently with products that can alter the pH of its base, such as topical lactic acid. When it is desirable to use multiple topical agents to achieve a clinical goal, patients may be instructed to apply the various medications at separate times throughout the day. Along with the option of concurrent use of topical agents, topical agents can be combined with either phototherapy or systemic agents to enhance efficacy in patients who are improving but still have areas of active disease.

Use of topical agents can be both intermittent and long-term. In general, it is recommended that more potent agents be used on a short-term basis to allow for response, after which patients should be instructed to use these agents intermittently for long-term management. This strategy may confer less risk of side effects than continuous treatment. Alternatively, patients who require continuous topical treatment 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. Although topical agents for psoriasis are usually well tolerated without significant side effects,[7] it is important that patients receive regular examinations, whether they use medications over the long term or intermittently as unsupervised use of potent topical medications is not recommended.

It is generally accepted that approximately 400 g of a topical agent is required to cover the entire body surface of an average-sized adult when used twice daily for 1 week.[8] Guidance regarding the appropriate amount of topical agents to be applied to affected skin derives from the concept of the fingertip unit (Fig 1, Table I),[9] which provides a means for patients to more accurately dose their topical medications.

Table I. Use of topical agents: The fingertip unit and how to assess quantity of topical agents needed to cover a given body surface area[79]

Area to be treated	No. of fingertip units	Approximate body surface area (%)
Scalp	3	6
Face and neck	2.5	5
One hand (front and back) including fingers	1	2
One entire arm including entire hand	4	8
Elbows (large plaque)	1	2
Both soles	1.5	3
One foot (dorsum and sole), including toes	1.5	3
One entire leg including entire foot	8	16
Buttocks	4	8
Knees (large plaque)	1	2
Trunk (anterior)	8	16
Trunk (posterior)	8	16
Genitalia	0.5	1

Adherence to topical treatment of psoriasis is a major issue, being generally poor in the majority of patients. Factors contributing to this include intolerance to medications, lack of response, poor choice of vehicle, and use of topical medications in the setting of extensive disease. Frustration with medication efficacy, inconvenience, and fear of side effects are also important factors.[10] Age of the patient and cost of the medications are other important variables affecting the patient's ability to adhere to a treatment regimen. Measures to improve patient adherence, including choosing topical medications with enough potency to achieve a favorable clinical response and individualizing the vehicle to allow for patient tolerance, are strongly encouraged.[11]

CORTICOSTEROIDS

Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis, particularly those with limited disease. They are available in many strengths and formulations, which allows for versatility of use. The mechanisms of action of corticosteroids include anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive effects. These effects are mediated through their binding to intracellular corticosteroid receptors and regulation of gene transcription of numerous genes, particularly those that code for proinflammatory cytokines. The potency ranking of topical

Table II. Efficacy of different classes of topical corticosteroids for the treatment of psoriasis

Class of topical steroid (1-7)	Range of efficacy rates	References
1 (superpotent)	58%-92%	Bernhard et al[13] (1991) Lebwohl et al[14] (2002) Gottlieb, Ford, and Spellman[15] (2003) Olsen et al[16] (1991)
2 (potent)	68%-74%	Savin[17] (1978) Lepaw[18] (1978)
3, 4 (midstrength and upper midstrength)	68%-72%	Olsen[19] (1996) Franz et al[20] (1999) Stein et al[21] (2001)
5, 6, 7* (least potent, midstrength, and lower midstrength)	41%-83%	Sears, Bailer, and Yeadon[22] (1997) Pauporte et al[23] (2004)

*Because of a lack of data for all 7 classes of topical steroids, in this table we have chosen to group the classes as shown above. Note that all but one of these trials were no longer than 4 weeks in duration.

steroids is based on their ability to produce vasoconstriction according to the Stoughton-Cornell classification system.[12] Topical steroids range in strength from weak, over-the-counter preparations, such as 1% hydrocortisone, to superpotent preparations, such as clobetasol propionate.

The choice of the appropriate potency corticosteroid and its vehicle should take into consideration the disease severity, the location being treated, patient preference, as well as the age of the patient. Lower potency corticosteroids should generally be used for limited periods of time on the face, intertriginous areas, areas with thin skin, and in infants. In other areas and in adults, mid- or high-potency agents are generally recommended as initial therapy. Patients with thick, chronic plaques often require treatment with the highest potency corticosteroids. For class I corticosteroids, the available data allow for 2 to 4 weeks of use with increased risk of both cutaneous side effects and systemic absorption if used continuously for longer periods of time. The optimal end point for the use of the less potent agents is not known. When topical corticosteroids are used to treat psoriasis, it is recommended that a gradual reduction in the frequency of usage following clinical response be instituted, although the exact details of this tapering are not well established. Many factors can alter the efficacy of topical corticosteroids, including the vehicle, the area of usage, the presence or absence of occlusion, patient preference, and the age of the patient.

Efficacy rates of the different classes of topical corticosteroids vary widely even among agents of the same class, ranging from 41% up to 92% (Table II). In addition, it is important to understand the specifics of the primary end point used in each study as this will have an important bearing on the percentage of improvement noted. There are 4 vehicle- or placebo-controlled trials of class I steroids. In a 2-week, double-blind, vehicle-controlled trial of 204 patients with moderate to severe psoriasis, those treated with halobetasol propionate ointment (class I) demonstrated a 92% improvement in physician's global assessment (PGA) compared with 39% of vehicle-treated patients ($P < .0003$).[13] A 2-week, double-blind, placebo-controlled trial of 81 patients with mild to moderate psoriasis demonstrated that 58% of patients treated with clobetasol foam (class I) achieved moderate or better improvement as compared to 15% of vehicle-treated patients ($P < .00005$),[14] whereas another 2-week, double-blind, placebo-controlled trial of 279 patients with mild to moderate psoriasis found that 68% of patients treated with clobetasol foam achieved clear or almost clear status compared to 21% of patients treated with vehicle ($P < .00001$).[15] In a double-blind, vehicle-controlled study of 378 patients with moderate to severe psoriasis treated with clobetasol solution (class I) for 2 weeks, 81% of patients treated with clobetasol solution compared to 22% of patients treated with vehicle achieved 50% or better clearing ($P = .0001$).[16] In a double-blind, vehicle-controlled study of 35 patients with psoriasis treated for 3 weeks with desoximetasone cream (class II), 68% of desoximetasone cream–treated patients compared to 23% of vehicle-treated patients achieved improvement in their mean overall evaluation scores ($P < .001$).[17] In another double-blind study of 27 patients with scalp psoriasis treated for 2 weeks, 74% of patients treated with halcinonide solution (class II) compared with 45% of patients treated with vehicle achieved excellent or good response ($P = .001$).[18] Two randomized vehicle-controlled studies of 383 patients with moderate to severe psoriasis revealed that 68% to 69% of patients treated with fluticasone propionate 0.005% ointment (class III) as compared with 29% to 30% of patients treated with vehicle for 4 weeks demonstrated good, excellent, or clear skin ($P = .00001$).[19] There are two placebo-controlled studies of betamethasone valerate foam (class IV). A 4-week, double-blind, placebo-controlled trial of 172 patients with moderate to severe scalp psoriasis demonstrated that 72% of patients treated with betamethasone valerate foam achieved improvement in the PGA as compared to 47% of placebo-treated patients[20] ($P < .05$). A 12-week, double-blind,

placebo-controlled trial of 40 patients with non-scalp psoriasis found that 70% of patients treated with betamethasone valerate foam (class IV) compared with 24% of patients treated with placebo achieved greater than 50% improvement ($P < .001$).[21] In a 3-week, double-blind, vehicle-controlled study of 190 patients with mild to moderate psoriasis, 41% of patients treated with hydrocortisone 17-butyrate 21-propionate cream (class V), achieved excellent or good improvement as compared to 18% of patients treated with vehicle cream ($P = .002$).[22] In a randomized, double-blind, vehicle-controlled, 3-week trial of 89 patients with severe scalp psoriasis, 83% of patients treated with fluocinolone acetonide 0.01% oil (class VI), compared with 36% of vehicle-treated patients had good or better improvement from baseline ($P < .001$).[23] Although double-blind, placebo-controlled trials represent the highest quality of evidence available to assess the efficacy of topical corticosteroids in the treatment of psoriasis, differences in study design, patient populations, and end points make it difficult to compare the vast array of published studies. However, in a large systematic review of topical corticosteroids for the treatment of psoriasis, potent and very potent topical corticosteroids were shown to be more efficacious than mild or moderate corticosteroids.[24]

A significant limitation of most clinical trials evaluating the safety and efficacy of topical corticosteroids for the treatment of psoriasis is the short duration of treatment of only several weeks, which does not allow for an assessment of the efficacy or the risks of longer term therapy. Furthermore, psoriasis invariably recurs after discontinuation of topical corticosteroid treatment. In studies where the class II corticosteroid betamethasone dipropionate ointment was discontinued abruptly, the mean duration of remission was 2 months.[25] Tachyphylaxis, defined as the loss of effectiveness with continued use, while not demonstrated in some studies,[26] may affect the long-term results achieved in a given patient. It remains controversial whether tachyphylaxis is a result of true loss of effectiveness of the medication, or whether it reflects a loss of compliance to therapy on the part of patients. Further investigation into this area is encouraged.

Precautions

Topical corticosteroids are associated with potential side effects that can limit their use. Local cutaneous side effects, which occur more frequently than systemic side effects, are more commonly seen at steroid-sensitive sites, including the face and intertriginous areas, as well as in any areas that are treated over the long term. These include skin atrophy, telangiectasia, striae distensae, acne, folliculitis, and purpura. Topical corticosteroids may exacerbate preexisting or coexistent dermatoses, such as rosacea, perioral dermatitis, and tinea infections and may on occasion cause contact dermatitis. Another possible concern with the use of topical corticosteroids in the treatment of psoriasis is rebound, wherein disease recurs worse than the pretreatment baseline after the topical corticosteroid is discontinued. Although rebound is known to occur most typically when topical corticosteroids are abruptly discontinued, its frequency and severity are poorly characterized. This is another area worthy of further investigation.

Systemic side effects, although infrequent, may occur when locally applied corticosteroids become absorbed through the skin and enter the circulatory system. The greatest risk of systemic side effects occurs when ultra-high-potency or high-potency corticosteroids are used over a large surface for a prolonged period or are used under occlusion, although systemic effects have also been observed with widespread and extended use of mid-potency corticosteroids. The continuous use of class I topical corticosteroids should normally be limited to no more than twice daily for up to 2 to 4 weeks and no more than 50 g/wk. This limitation is based on the evidence available from controlled studies and detailed in package inserts. However, longer durations of therapy are frequently utilized in clinical practice with appropriate supervision and attention to potential side effects. Well-known but relatively uncommon systemic side effects of topical corticosteroid usage include Cushing's syndrome, osteonecrosis of the femoral head, cataracts, and glaucoma. Although symptomatic hypothalamic-pituitary-adrenal (HPA) axis suppression is a relatively uncommon side effect of topical corticosteroids, laboratory evidence for HPA axis suppression is more common in patients treated with more potent topical corticosteroids. In two distinct studies, 20% of patients treated with clobetasol ointment (class I)[27] had laboratory evidence for HPA suppression compared to 3% of patients treated with desonide ointment (class VI).[28] Infants and younger children are at increased risk of local and systemic side effects, including growth retardation as a result of their higher skin surface to body mass ratio. All of the topical corticosteroids are pregnancy category C and are of unknown safety in nursing women. Several approaches have been utilized to minimize the side effects of topical corticosteroids, including transitioning to weaker potency agents after clinical improvement, intermittent usage (weekend only), and combination with other

Table III. Recommendations for topical corticosteroids

- Indication: Plaque-type psoriasis
- Dosing:
  - Can be used as monotherapy 1-2 times daily
  - Can be combined with other topical agents, UV light, and systemic agents
- Potency of topical steroids
  - Stoughton-Cornell classification system divides steroids into 7 classes.
- Duration of dosing:
  - Class I steroids: available data for 2-4 weeks of treatment
  - Less potent agents: optimal end point unknown
  - Gradual reduction in usage recommended following clinical response; while optimal end point is unknown, unsupervised continuous use is not recommended.
  - For clobetasol and halobetasol, maximal weekly use should be 50 g or less
- Short-term results:
  - Highly potent agents have greater efficacy than less potent agents.
  - Vehicle, usage area, patient preference, patient age, and cost after efficacy
  - See Table I for efficacy rates.
- Long-term results:
  - True efficacy and risks associated with long-term use are unknown as most clinical trials are of short duration.
  - Tachyphylaxis, while not demonstrated in clinical trials, may affect the long-term results achieved in a given patient.
  - Combination with other topicals and variations in dosing schedules may lessen risk of long-term side effects.
- Toxicities:
  - Local—skin atrophy, telangiectasia, striae, purpura, contact dermatitis, rosacea
  - Systemic—hypothalamic-pituitary-adrenal axis suppression may occur with use of medium- and high-potency topical steroids. This will be lessened by intermittent or localized use. Unilateral or bilateral avascular necrosis of the femoral head rarely occurs. Increased intraocular pressure, glaucoma, and cataracts have been reported with use around the eye.
  - Risks increase when used with excessive frequency or duration.
  - It is unknown if there is an increased risk of infection with long-term use.
- Baseline monitoring: None
- Ongoing monitoring:
  - Assessment of growth in children using topical corticosteroids for long term
  - Regular skin checks for all patients receiving long-term therapy to assess for atrophy
- Pregnancy: Category C
- Nursing: Unknown safety
- Pediatric use: Because of the increased skin surface/body mass ratio, the risks to infants and children may be higher for systemic effects secondary to enhanced absorption. Growth retardation is also a potential concern.

nonsteroidal agents (see below). Recommendations for the use of topical corticosteroids are shown in Table III. The strength of recommendations for the treatment of psoriasis using topical corticosteroids is also shown in Table IV.

Although corticosteroids remain the mainstay of topical therapy for psoriasis, the most potent and efficacious of these agents are approved for only a short-term treatment (2-4 weeks). However, since potent corticosteroids are often used in the longer term in clinical practice, such patients should be carefully monitored to detect possible side effects at the earliest stage. In addition, consideration should be given to the use of medications that have been developed that are meant either to replace potent topical corticosteroids in longer term treatment or to be used in combination to provide greater efficacy with lesser exposure to steroid-containing agents. Pursuit of these goals with agents including vitamin D analogues, topical retinoids, and calcineurin inhibitors has shown benefit.

VITAMIN D ANALOGUES

Calcipotriol (calcipotriene), a synthetic vitamin D analogue, was first introduced in the early 1990's in Europe to treat psoriasis and is now available in the United States. The potential role of vitamin D analogues in the treatment of psoriasis derived from the observation that a patient being treated with oral vitamin D experienced significant improvement in his psoriasis.[29] The mechanism of action of the vitamin D analogues in psoriasis is believed to be mediated by their binding to vitamin D receptors, which leads to both the inhibition of keratinocyte proliferation and the enhancement of keratinocyte differentiation.

Table IV. Strength of recommendations for the treatment of psoriasis using topical therapies*

Agent	Strength of recommendation	Level of evidence	References
Class I corticosteroids	A	I	13-16, 73
Class II corticosteroids	B	II	17, 18
Class III/IV corticosteroids	A	I	19-21, 72
Class V/VI/VII corticosteroids	A	I	22, 23
Vitamin D analogues	A	I	30, 32, 37, 38, 72, 73
Tazarotene	A	I	39, 40, 75
Tacrolimus and pimecrolimus	B	II	43, 44, 77, 78
Anthralin	C	III	54, 55
Coal tar	B	II	56, 57
Combination corticosteroid and salicylic acid	B	II	63
Combination corticosteroid and vitamin D analogue	A	I	37, 38, 64-66
Combination corticosteroid and tazarotene	A	I	67-69
Combination tacrolimus and salicylic acid	B	II	71

*Although there are two controlled studies that evaluate the efficacy of one nonmedicated moisturizer (aloe vera gel), the results of these studies are contradictory; therefore no strength of recommendations for its use is included in this table. As there are also no controlled studies evaluating the efficacy of salicylic acid, no strength of recommendations for its use is included in the table.

Until recently, calcipotriene has been available in cream, ointment, and solution formulations. With the recent advent of a combination product containing both calcipotriene and betamethasone propionate ointment, calcipotriene ointment is no longer commercially available as an individual product in the United States. In a randomized, placebo-controlled trial, 70% of patients with plaque psoriasis involving 5% to 20% body surface area treated with calcipotriene ointment showed greater than 75% improvement in their plaque psoriasis as compared to 19% of vehicle-treated patients.[30] In a double-blind, right-left comparison trial, 74% of patients treated with calcipotriol showed marked improvement or clearing as compared with 18% of patients treated with vehicle.[31] For scalp psoriasis, 60% of patients treated with calcipotriene solution showed clearance or marked improvement of their scalp psoriasis as compared to 17% of vehicle-treated patients in a randomized, placebo-controlled trial.[32]

Calcitriol (the active metabolite of vitamin D) and tacalcitol, another synthetic vitamin D analogue, are available outside of the United States for the treatment of psoriasis, with the former expected to gain approval imminently in the United States. Tacalcitol is dosed once daily while calcitriol has better tolerability in readily irritated areas of the skin, including the face, hairline, and flexural areas.[31] Other vitamin D analogues, including maxacalcitol and becocalcidiol, are also being studied for the treatment of psoriasis.

Precautions

Local side effects, which may occur both on the treated lesions as well as perilesionally, can affect up to 35% of patients and may include burning, pruritus, edema, peeling, dryness, and erythema. With ongoing treatment, these side effects are often mitigated. Systemic side effects due to topical vitamin D analogues, which can include hypercalcemia and parathyroid hormone suppression, are quite rare unless patients are applying more than the recommended dosage of 100 g/wk or have underlying renal disease or impaired calcium metabolism. While there is some evidence that calcipotriene can be photosensitizing, presumably due to thinning of the epidermis, significant experience demonstrates that there are no contraindications to combining calcipotriene with UVB phototherapy.[33,34] However, since calcipotriene is inactivated by UVA, it is important to apply calcipotriene after and not before UVA exposure. All formulations of calcipotriene are pregnancy category C. There is no information on the excretion into breast milk, and pregnant and nursing mothers were excluded from the clinical studies. Use of calcipotriene in children (studied in ages 2-14 years) is effective and well tolerated with mild skin irritation and no metabolic effects noted at dosages up to 50 g/wk.[35,36] Recommendations for the use of vitamin D analogues are shown in Table V. The strength of recommendations for the treatment of psoriasis using topical vitamin D analogues are shown in Table IV.

COMBINATION CALCIPOTRIENE/BETAMETHASONE PROPIONATE OINTMENT

An important advantage of the vitamin D analogues is their potential to function in a corticosteroid-sparing fashion. This observation has led to the

Table V. Recommendations for vitamin D analogues

- Indication: Plaque-type psoriasis
- Dosing: Twice daily to affected areas
- Efficacy:
  - In two large studies of plaque-type psoriasis of the body, 70% to 74% of patients treated with calcitriol or calcipotriene ointment showed either 75% improvement or marked improvement to clearing as compared with 18% to 19% of patients treated with placebo. Sixty percent of scalp psoriasis patients treated with calcipotriene solution showed clearance or marked improvement as compared with 17% of placebo patients.
  - Combination of calcipotriene and betamethasone ointment: In a 4-week trial of patients with mild to severe plaque psoriasis, 48% of patients treated with the combination agent achieved absent or mild psoriasis, compared with 16.5% of patients treated with calcipotriene once daily, 26.3% of patients treated with betamethasone once daily, and 7.6% of patients treated with placebo. A 52-week clinical practice dosage study showed 70% to 80% of patients achieving clear or almost clear status with no drug-related serious adverse events, such as HPA axis oppression or striae when used on an as-needed basis.
- Use in combination with topical corticosteroids gives added benefit.
- Contraindications/adverse reactions:
  - Irritation in lesional and perilesional skin that is transient
  - Reversible elevation of serum calcium—more likely to occur patients treated with greater than 100 g/wk.
  - Causes photosensitivity, but no contraindications to combining with UVB phototherapy; when using combination calcipotriene/betamethasone, the side effects of high-potency topical corticosteroids including HPA axis suppression, skin atrophy, among others (see above) may occasionally occur.
- Pregnancy and nursing:
  - Category C
  - No information on excretion in breast milk; pregnant and nursing mothers were excluded from clinical studies.
- Pediatric use: Appears to be safe

HPA, Hypothalamic-pituitary-adrenal (axis).

development of a single-agent combination product for the treatment of patients with psoriasis. In short-term trials of 4 weeks' duration, which included 1603 patients with mild to severe psoriasis, 48% of patients treated with the combination of calcipotriene 0.005% ointment and betamethasone propionate 0.064% ointment once or twice daily achieved an end point of absent to mild disease, which compared favorably to patients treated with either calcipotriene alone (16.5%) or those treated with betamethasone alone (26.3%).[37] In a long-term 52-week usage study of 828 patients, 69% to 74% of patients treated with the combination of calcipotriene 0.005% and betamethasone 0.064% once or twice daily achieved clear or almost clear status compared to 27% of the patients in the placebo group ($P < .001$). There were no drug-related serious adverse events, including striae or HPA axis suppression, observed when combination calcipotriene 0.005% and betamethasone 0.064% were used over the 52-week period on an as needed basis.[38]

TAZAROTENE

Although oral retinoids have been used in the treatment of psoriasis for many years, the topical retinoid tazarotene first became available for the treatment of psoriasis in 1997. Tazarotene is thought to function by normalizing abnormal keratinocyte differentiation, diminishing hyperproliferation, and by decreasing expression of inflammatory markers. In a vehicle-controlled trial of 318 patients with plaque psoriasis, success rates, defined as 50% or more improvement, were seen in 63% and 50% of patients treated with tazarotene 0.1% gel and 0.05% gel, respectively, compared with 31% of patients treated with vehicle once daily for 12 weeks ($P < .05$ for both concentrations compared to vehicle).[39] In two large vehicle-controlled trials of 1303 patients with plaque psoriasis, success rates defined as overall lesional assessment of none, minimal, or mild were 40% to 51% for tazarotene 0.1% cream and 0.05% cream compared to 25% of patients treated with vehicle once daily for 12 weeks ($P < .04$ for both concentrations compared to vehicle).[40]

Precautions

The most common side effect of tazarotene is local irritation in lesional and perilesional skin. Irritation may be reduced by use of the cream formulation, use of the lower concentration product, combination use with moisturizers, application on alternate days, short-contact (30 to 60 minutes) treatment,[41] and applying in combination with topical corticosteroids (see below). Although tazarotene is potentially photosensitizing (due to thinning of the epidermis) and caution should be used when combining this

treatment with phototherapy, a randomized controlled study evaluating the combination of tazarotene and UVB not only showed a significant enhancement of the efficacy of phototherapy, but also greatly diminished the amount of ultraviolet exposure needed to obtain a good clinical response.[42] Tazarotene is a teratogenic retinoid and is pregnancy category X; therefore use in pregnancy must be avoided. It is known to be excreted in mouse milk, but it is unclear what quantity of tazarotene is excreted in human milk. There are no available data regarding the use of tazarotene in patients with psoriasis under the age of 18, although in the treatment of acne, tazarotene is approved for children 12 years of age and older. Recommendations for the use of tazarotene are shown in Table VI. The strength of recommendations for the treatment of psoriasis using topical tazarotene is shown in Table IV.

Table VI. Recommendations for topical tazarotene

- Indication: Plaque-type psoriasis
- Dosing: Applied once daily
- Efficacy: 50% or more improvement, seen in 63% and 50% of patients treated with tazarotene 0.1% gel and 0.05% gel, respectively, once daily for 12 weeks, compared with 31% of patients treated with vehicle; overall lesional assessment of none, minimal, or mild found in 50% to 51% of patients treated with tazarotene 0.1% cream and 0.05% cream used once daily for 12 weeks, compared with 25% of patients treated with vehicle
- Best used in combination with topical corticosteroids
- Contraindications/adverse reactions:
  - Most common side effect is skin irritation in lesional and perilesional skin.
  - Photosensitizing
- Pregnancy and nursing:
  - Pregnancy category X
  - Excreted in mammalian milk, but quantity in human milk is unclear
- Pediatric use: No available data in psoriasis in patients younger than 18 years of age; for acne, approved to age 12 years

TACROLIMUS AND PIMECROLIMUS

The topical calcineurin inhibitors tacrolimus and pimecrolimus have been available to treat atopic dermatitis in adults and children over the age of 2 since 2000 and 2001, respectively. Calcineurin inhibitors function by blocking the synthesis of numerous inflammatory cytokines that play an important role in the pathogenesis of psoriasis. When first studied in their commercially available forms for chronic plaque psoriasis, neither pimecrolimus nor tacrolimus were effective therapies. Both of these agents demonstrated efficacy in the treatment of plaque psoriasis when they were used under occlusion, suggesting that there was a lack of penetration through the thick psoriatic plaque. This led to the concept of utilizing the topical calcineurin inhibitors in thinner skin areas such as facial and intertriginous psoriasis with no evidence of resultant skin atrophy as compared with the use of topical corticosteroids in these regions. In a double-blind, randomized, vehicle-controlled study of 167 patients with facial and intertriginous psoriasis, 65% of patients treated with tacrolimus 0.1% ointment were clear or almost clear after 8 weeks of therapy as compared with 31% of patients treated with placebo.[43] In a double-blind, randomized, vehicle-controlled study of 57 patients with intertriginous psoriasis, 71% of the patients treated with pimecrolimus 0.1% cream were clear or almost clear after 8 weeks of twice-daily treatment as compared with 21% of patients treated with placebo.[44]

Precautions

There are no specific precautions for the use of topical calcineurin inhibitors in the treatment of psoriasis; however, it should be noted that all information available is derived from their use in atopic dermatitis. The most common side effect for both medications is burning and itching that generally reduces with ongoing usage and can also be mitigated by not applying immediately after bathing. This side effect appears to be more significant in patients treated with tacrolimus ointment as compared with patients treated with pimecrolimus cream. In 2005, the Food and Drug Administration implemented a "black box" warning for tacrolimus ointment[45] and pimecrolimus cream[46] because of the lack of long-term safety data and the potential risk for the development of malignancies. However, clinical evidence to date does not reveal any causal link between an increased risk of cancer and the use of either of the topical calcineurin inhibitors.[47] Although some animal studies suggest that the concomitant use of calcineurin inhibitors and ultraviolet light may lead to an increased risk of epithelial tumors, there are no similar observations in humans.[48,49] Prudence would therefore dictate cautious use of topical calcineurin inhibitors in patients with psoriasis who are being treated with ultraviolet light. Both pimecrolimus and tacrolimus are pregnancy category C, are found in human milk, and thus are not recommended for nursing mothers. Topical tacrolimus (0.03%) ointment and topical pimecrolimus cream are approved for patients as young as 2 years of age with atopic dermatitis. Recommendations for the use of tacrolimus and

Table VII. Recommendations for topical tacrolimus and pimecrolimus

- Indications: No FDA-approved indications for psoriasis; primary indications for off-label use are for facial and intertriginous psoriasis.
- Dosing: Applied twice daily to affected areas; no duration of course is specified.
- Efficacy:
  - Plaque psoriasis: Not generally effective
  - Intertriginous and facial psoriasis: 65% of patients treated with tacrolimus 0.1% ointment were clear or almost clear after 8 weeks of therapy compared with 31% of patients treated with placebo; 71% of the patients treated with pimecrolimus 0.1% cream were clear or almost clear after 8 weeks of therapy as compared with 21% of patients treated with placebo.
- Contraindications/adverse reactions:
  - There are no specific contraindications/adverse reactions for psoriasis.
  - Most common side effect for both medications is burning and itching.
  - A controversial lymphoma "black box" warning has been issued by the FDA.
- Pregnancy and nursing:
  - Category C
  - Tacrolimus and pimecrolimus are found in human milk and are not recommended for nursing mothers.
- Pediatric use: Topical tacrolimus (0.03%) and topical pimecrolimus are approved for patients 2 years of age or older for atopic dermatitis.

FDA, Food and Drug Administration.

pimecrolimus are shown in Table VII. The strength of recommendations for the treatment of psoriasis using topical tacrolimus and pimecrolimus are shown in Table IV.

OTHER TOPICAL TREATMENTS

Non-medicated topical moisturizers

The use of non-medicated topical moisturizers (which may include occlusive agents, emollients, and humectants) represents an internationally accepted standard adjunctive therapeutic approach to the treatment of psoriasis.[4] Of the 11 topical steroids trials discussed above, the vehicle/placebo response rate ranged from 15% to 47%, suggesting a beneficial effect of moisturizers in general. There are two randomized placebo-controlled trials of aloe vera gel for the treatment of mild to moderate psoriasis with one showing beneficial effects[50] and the other showing no benefit over placebo.[51] There are numerous other non-medicated topical moisturizer compounds and formulations available; depending on the individual product, they can be applied up to several times daily. The goal of treatment with these agents is to provide and retain moisture in the stratum corneum; these agents are thought to function by forming a film on the skin surface to help retain moisture. There are no known contraindications to the use of these non-medicated moisturizers; the large majority of these agents are considered safe during pregnancy and lactation as well as for pediatric use. Recommendations for the use of emollients are shown in Table VIII.

Table VIII. Recommendations for emollients

- Indications: The use of emollients represents an internationally accepted standard adjunctive therapeutic approach to the treatment of psoriasis.
- Dosing: Applied once to 3 times daily
- Efficacy: Two controlled studies of aloe vera had conflicting results.
- Contraindications/adverse reactions: No known contraindications
- Pregnancy and nursing: Generally considered safe
- Pediatric use: Generally considered safe

Salicylic acid

Salicylic acid is a topical keratolytic agent that has been used for many years in the topical treatment of psoriasis. While the precise mechanism of keratolysis is not fully understood, it is thought that salicylic acid may reduce keratinocyte-to-keratinocyte binding as well as reduce the pH of the stratum corneum; these effects lead to reduced scaling and softening of psoriatic plaques.[52] 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 corticosteroids and topical immunomodulators (see below). The improvements in efficacy of combination therapy compared with salicylic acid alone are likely due to the increased skin penetration that occurs because of the keratolytic effects of salicylic acid. Combination agents containing both salicylic acid and topical corticosteroids are not currently available in the United States.

Precautions. Because of a risk of systemic toxicity, topical salicylic acid should not be used in combination with other oral salicylate drugs. Systemic absorption of topical salicylate, although rare, can occur, especially when it is applied to more than 20% of the body surface or in patients with abnormal hepatic or renal function. Topical salicylic acid decreases the efficacy of UVB phototherapy because of a filtering effect; it therefore should not be applied before UVB phototherapy. Salicylic acid appears to be a safe choice for the control of

Table IX. Recommendations for salicylic acid

- Indications: No specific FDA indication
- Dosing: Applied daily
- Efficacy: Data are limited on salicylic acid used alone.
  - Comparator study of tacrolimus and salicylic acid versus tacrolimus alone in small study (N = 24) of psoriasis patients with <10% BSA revealed improved efficacy with addition of salicylic acid
  - Comparator study of 408 patients with moderate to severe psoriasis treated with mometasone and salicylic acid versus mometasone alone for 3 weeks; psoriasis severity index measure erythema, induration, and scaling showed the combination of mometasone furoate—salicylic acid to be more effective than mometasone furoate alone.
- Contraindications/adverse reactions: Do not combine salicylic acid with other salicylate drugs. Systemic absorption, although rare, can occur, especially when applied to more than 20% of BSA or in patients with abnormal hepatic or renal function. Salicylic acid decreases the efficacy of UVB phototherapy because of a filtering effect and should not be used before UVB phototherapy.
- Pregnancy/nursing: Appears to be a safe choice for the control of localized psoriasis in pregnancy
- Pediatric use: Because of greater risk of systemic absorption and toxicity, salicylic acid should be avoided in children.

BSA, Body surface area.

localized psoriasis in pregnancy; however, because of a greater risk of systemic absorption and toxicity, salicylic acid should be avoided in the treatment of children. Recommendations for the use of salicylic acid are shown in Table IX.

Anthralin

While anthralin used to be a mainstay for the topical treatment of psoriasis, typically in the inpatient setting, its use has declined in recent years because of the availability of more cosmetically acceptable alternatives. Although the exact mechanism of action of anthralin is not fully understood, recent studies suggest that its ability to prevent T-lymphocyte activation and normalize keratinocyte differentiation may occur by a direct effect on mitochondria.[53] In the two small placebo-controlled studies of the efficacy of anthralin as monotherapy for 12 and 27 patients, a totally aqueous gel formulation of dithranol, in increasing concentrations as tolerated up to as high as 2%, when applied twice daily after 4 weeks, and 1 minute of treatment with 2% dithranol ointment daily for 3 weeks both demonstrated significantly better results than placebo in the treatment of psoriasis.[54,55] Several doses and preparations of anthralin are available; however, owing largely to issues of cosmesis and convenience, anthralin is most commonly used as short contact (20-30 minutes) therapy in the outpatient setting, starting at 1% concentration with increasing concentration over time as tolerated.

Table X. Recommendations for anthralin

- Indications: Was important component of psoriasis treatment for many years
- Dosing: Several doses are available; now commonly used as short-contact therapy, starting at 1% concentration with increasing concentration over time as tolerated.
- Efficacy: Limited placebo-controlled trial data, but as monotherapy, anthralin appears to have lower efficacy than more potent topical corticosteroids or vitamin D derivatives.
- Contraindications/adverse reactions: Most common side effects are skin irritation and staining of the skin and other touching objects. Because of skin irritation, it is important to avoid contact with surrounding normal skin.
- Pregnancy/nursing: Category C
- Pediatric use: Use with caution.

Precautions. The most common side effects of anthralin are skin irritation and staining of lesional and adjoining skin, nails, clothing, and other objects with which patients come into contact. The frequency of irritation of affected as well as surrounding unaffected skin is greater in patients who leave anthralin on the skin without washing it off than in those who are treated with short-contact therapy (exposure to anthralin for 2 hours or less). 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. Anthralin should be applied with caution to face and intertriginous areas because of the risk for severe skin irritation. There is no evidence of any long-term toxicities related either to skin exposure or to systemic issues. Optimal regimens utilizing anthralin require careful balancing of time of exposure as well as the concentration of anthralin. Anthralin is pregnancy category C. Recommendations for the use of anthralin are shown in Table X. The strength of recommendations for the treatment of psoriasis using topical anthralin is shown in Table IV.

Coal tar

Coal tar, a distillation product from coal, is a mixture of thousands of compounds which may differ in composition from one preparation to the next. Coal tar has been used since ancient times for the treatment of various skin diseases and for approximately 100 years in the treatment of psoriasis.

Table XI. Recommendations for coal tar

- Indications: Used in the treatment of psoriasis for more than 100 years; although the use of tar products for treatment of localized psoriasis has decreased over time in the U.S., they are still often used in other countries.
- Dosing: Many formulations exist.
- Efficacy: In double-blind, randomized, controlled trial of 324 patients with mild to moderate psoriasis comparing 1% coal tar lotion with 5% coal tar extract, there was better improvement in both PASI score and TSS in patients treated with 1% lotion than in 5% extract.
- Contraindications/adverse reactions: Often poorly tolerated by patients because of cosmetic issues, including staining of clothes and tar odor; other potential adverse events include irritant contact dermatitis, folliculitis, and photosensitivity. Coal tar is carcinogenic in animals, but in humans, there are no convincing data proving carcinogenicity, and epidemiologic studies fail to show increased risk of skin cancer in patients who use coal tar.
- Pregnancy/nursing: Risk of topical coal tar used for brief periods of time during pregnancy is likely to be small.
- Pediatric use: Use with caution.

PASI, Psoriasis Area and Severity Index.

Although the mechanism of action of coal tar is not well understood, it is known to suppress DNA synthesis by lessening the mitotic labeling index of keratinocytes. The Goeckerman regimen, which consists of the combination of crude coal tar along with ultraviolet light used in the inpatient setting, was first described in 1925. The modified Goeckerman regimen, performed in the outpatient setting, is a very effective treatment for patients with severe psoriasis. Although the use of tar products for treatment of localized psoriasis has decreased over time in the United States, they are still often used outside the United States. Many formulations of coal tar exist, and standardization of these products is not always ideal. In one small study of 18 patients, 5% liquor carbonis detergens was more effective than its emollient base in the treatment of psoriasis.[56] In a double-blind, randomized, controlled trial of 324 patients with mild to moderate psoriasis that compared 1% coal tar lotion with 5% coal tar extract, there was better improvement in both PASI (Psoriasis Area and Severity Index) score and total sign score in patients treated with 1% lotion than with 5% extract.[57]

Precautions. Coal tar products are often poorly tolerated by patients because of cosmetic issues, including staining of clothes and the tar odor that is present in almost all products. Other potential adverse effects include irritant contact dermatitis, folliculitis, and photosensitivity to UVA. Coal tar is carcinogenic in animals; however, in humans there are no convincing data proving carcinogenicity, and epidemiologic studies fail to show increased risk of skin cancer in patients who use coal tar. Although occupational exposure to coal tar may increase the risk of lung cancer, scrotal cancer, and skin cancer, patients with psoriasis or atopic dermatitis who are treated with coal tar products applied to the skin do not have an increased risk of cancer.[58-60] One small retrospective study of 17 infants delivered from women who had been treated with topical coal tar during pregnancy found one infant born with a lethal trisomy 13.[61] Based on these limited data, a recent review of the literature concluded that the risk of topical coal tar used for short periods of time during pregnancy is likely to be small.[62] Coal tar should be used with caution in the pediatric population. Recommendations for the use of coal tar are shown in Table XI. The strength of recommendations for the treatment of psoriasis using topical coal tar is shown in Table IV.

COMBINATION OF TOPICAL THERAPIES

Since all topical medications for the treatment of psoriasis have limitations, combination regimens, utilizing medications from different categories, have been studied and shown to be potentially beneficial.

Corticosteroids and salicylic acid

The combination of topical corticosteroids and salicylic acid may be valuable because of the ability of salicylic acid to enhance the efficacy of corticosteroids by increasing penetration.[63] To ensure that there is not an increase in steroid toxicities when adding salicylic acid to topical corticosteroid preparations, it is recommended that this combination be limited to no more than medium-potency (class 3-4) topical corticosteroids. The strength of recommendations for the treatment of psoriasis using topical corticosteroids and salicylic acid is shown in Table IV.

Corticosteroids and vitamin D analogues

The combination of topical corticosteroids and vitamin D analogues appears to be more efficacious than either therapy alone, with fewer side effects noted in most, but not all, studies.[7] This point has been demonstrated for several different corticosteroid-calcipotriol combinations[64-66] (please also see prior section on combination calcipotriene/betamethasone ointment). The strength of recommendations for the treatment of psoriasis using topical corticosteroids and vitamin D analogues is shown in Table IV.

Corticosteroids and tazarotene

Owing to the potential irritancy of topical tazarotene, adding topical corticosteroids to a regimen of tazarotene is an appropriate option. In fact, one study has shown that the combination of tazarotene and either mid- or high-potency topical corticosteroid is more effective than therapy with tazarotene alone; however, this study did not determine if tazarotene plus topical steroid is superior to topical corticosteroid alone.[67] There may be a synergistic effect between tazarotene and topical corticosteroids as a clinical trial comparing tazarotene gel plus mometasone cream to mometasone cream alone showed superior efficacy of the combination over mometasone cream used alone both for efficacy during the therapy and for the duration of therapeutic effect.[68] Combination therapy may increase the duration of treatment benefit as well as length of remission.[69] Another potential advantage of using combination tazarotene and topical corticosteroid is a potential decrease in steroid-induced atrophy.[70] The strength of recommendations for the treatment of psoriasis using topical corticosteroids and tazarotene is shown in Table IV.

Tacrolimus and salicylic acid

A comparator study of tacrolimus 0.1% ointment and 6% salicylic acid compared to tacrolimus alone in a small study of 24 patients with psoriasis with less than 10% body surface area involvement revealed improved efficacy with the addition of salicylic acid.[71] The strength of recommendations for the treatment of psoriasis using topical corticosteroids with tacrolimus and salicylic acid is shown in Table IV.

COMPARISON STUDIES OF TOPICAL THERAPIES

Vitamin D analogues

When calcipotriol was compared with betamethasone valerate ointment (class 3) in a randomized, double-blind, 6-week, right-left comparison trial, there was a 69% reduction in the mean PASI score of patients treated with calcipotriol compared to 61% reduction in mean PASI score of patients treated with betamethasone valerate ($P < .001$).[72] While vitamin D analogues usually have a slower onset of action than topical corticosteroids, they tend to yield longer disease-free periods. Thus, one randomized double-blind study demonstrated that 48% of patients with psoriasis treated with calcitriol ointment remained in remission as compared to 25% of patients treated with betamethasone dipropionate ointment.[73] A systematic review of the efficacy and tolerability of calcipotriol revealed that it is more effective for mild to moderate chronic plaque psoriasis than either coal tar or short-contact anthralin and that only potent topical corticosteroids have comparable efficacy at 8 weeks of treatment.[74] These authors noted that, although calcipotriol is more irritating than topical corticosteroids, this observation must be weighed against the known potential long-term toxicities of corticosteroids.

Tazarotene

When both strengths of tazarotene gel dosed once daily were compared to twice-daily fluocinonide 0.05% cream in a 12-week, multicenter, investigator-masked, randomized, parallel group trial, there was no significant difference in the efficacy of these therapies[75]; however, tazarotene demonstrated significantly better maintenance of therapeutic effect after discontinuation of therapy. In a multicenter, investigator-blinded study evaluating the safety and efficacy of tazarotene 0.1% gel plus mometasone furoate 0.1% cream (class IV) once daily to calcipotriene 0.005% ointment twice daily, patients treated with tazarotene plus mometasone achieved significantly greater reductions in body surface area involvement than did patients treated with calcipotriene alone.[76]

Tacrolimus and pimecrolimus

In a 6-week randomized, double-blind study of 50 patients with intertriginous and facial psoriasis, tacrolimus was more effective than calcitriol.[77] In a 4-week, randomized, double-blind, placebo-controlled trial of 80 patients with intertriginous psoriasis, pimecrolimus was less efficacious than both calcipotriol and betamethasone.[78]

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