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Topical Antipsoriatics

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ABSTRACT

Topical corticosteroids are important in psoriasis therapy. However, there are other worthwhile options available including tar, anthralin, tazarotene, calcipotriol, topical PUVA, and topical porphyrin derivatives. With growing public reluctance to use systemic medications, topical treatments for psoriasis could become increasingly important in the future.

KEY WORDS: *anthralin, calcipotriol, corticosteroids, psoriasis, PUVA, tar, tazarotene*

There have been advances in psoriasis therapy, but topical corticosteroids remain an important part of the treatment program. These drugs are useful not only to control this disease, but also to limit the irritation caused by medications such as tazarotene and anthralin. Ultrapotent topical corticosteroids can also be valuable for reducing the discomfort of acute UV light burns, a complication of UV light treatment[1].

Anthralin

Anthralin penetrates preferentially into the abnormal stratum corneum of psoriatic lesions after short exposure (e.g., 30 minutes), sparing the adjacent normal skin. This facilitates "short contact" anthralin therapy[6]. The major side effects of anthralin therapy, (i.e., erythema, skin irritation and staining of skin and clothing) can be reduced[7]. Patients should be instructed to wash anthralin cream off with cool water and no soap, because hot water and soap will liberate this drug from the liposomes in the cream, resulting in staining and irritation to normal skin.

Suggested mechanisms of action for anthralin include:

- generation of free radicals
- inhibition of DNA synthesis
- alteration of the epidermal growth factor receptor pathway
- alteration in mitochondrial respiratory function[8].

Tazarotene

Tazarotene gel is a retinoid that is rapidly converted in the skin to its active metabolite tazarotenic acid. This acid then selectively binds to the gamma and beta retinoic acid receptors that moderate the abnormal keratinocyte differentiation and hyperproliferation, as well as the increased inflammation associated with psoriasis. The onset of action is slower than with topical corticosteroids, but tazarotene, in some cases, can induce several months of remission, during which no treatment is needed[9]. Patients using tazarotene must be carefully instructed in the correct use of this medication, with particular emphasis on applying tazarotene only to thick scaly areas, and discontinuing tazarotene once the skin has become flat and nonscaly. We recommend the application of an appropriate mid potency corticosteroid later in the day for reducing irritation from the tazarotene, and speeding up resolution of the psoriasis.

Tazarotene is usually very well tolerated on the scalp, perhaps because of the numerous sebaceous glands on the scalp that help to reduce the dryness. Dryness can be a problem when tazarotene is applied to other parts of the body.

Drug	Therapy (mono or combined)	Side effects	Course of disease
Anthralin • *Micanol 1% Cream* • *Drithrocreme 1%*	Ointment – mono	Sensitivity, irritation, allergy, rash	Chronic treatment Can induce long remissions
Tazarotene • *Tazorac*	Monotherapy or used with corticosteroids or UVB	Retinoid reaction	Sometimes in remission for months
Calcipotriol • *Dovonex* • *Daivonex*	Used with UVB or with adrenocorticosteroids	Dermatitis, flare of psoriasis	Chronic treatment
Corticosteroids • *Potent (very high)* • *High* • *Plus salicylic acid**	Monotherapy–intermittent or combined with all other treatments	Skin atrophy, telangiectasis, rare systemic effects	Chronic treatment Rebound effect when treatment is discontinued
Crude coal tar	Used with salicylic acid or sulfur	Stings, stinks, stains, photosensitive	Chronic treatment

Table 1 – Current psoriasis treatments.
*Urea is preferred. It works just as well, and won't degrade calcipotriol.

Calcipotriol– Calcipotriene***

Calcipotriol *(Dovonex, Daivonex)* is an analogue of vitamin D that has minimal effects on system calcium metabolism. It is available as cream, ointment and lotion, and its antipsoriatic effect is likely mediated by inhibition of keratinocyte differentiation/proliferation, and by inhibition of T-lymphocyte activation[10]. Calcipotriol is usually well tolerated, but can occasionally cause irritation, especially if applied to the face or genital area. To reduce the risk of hypercalcemia the total amount applied should be less than 100gm per week. Tachyphylaxis to calcipotriol has not been observed, and this drug is safe for long-term use.

Salicylic acid instantly degrades calcipotriol. Therefore, when extemporaneous compounds are formulated, it is important to avoid using topical salicylic acid preparations at the same time as calcipotriol. Urea, however, does not cause degradation of calcipotriol[3].

Drugs	Plaque psoriasis	Nail psoriasis	Scalp psoriasis
Anthralin • *Micanol 1% Cream* • *Drithrocreme 1%*	Yes	No	Yes
Tazarotene •*Tazorac*	Yes	Yes	Yes
Cacipotriol • *Dovonex* • *Daivonex*	Yes	Yes – when mixed with 10% urea	Yes
Corticosteroids • *Potent (very high)* • *High* • *Plus salicylic acid*	Yes	Yes	Yes
Crude Coal Tar	Yes	No	Yes

Table 2 – Site treatment recommendations.

Corticosteroids

To reduce the total amount of topical corticosteroids required for psoriasis control, patients are often advised to use noncorticosteroid therapies. These can include other topical medications, UV light treatment, and systemic medications like methotrexate, acitretin *(Soriatane),* or cyclosporine *(Neoral)*. Conversely, patients taking these treatments are often well advised to continue with topical corticosteroids, thus reducing the amount of systemic medication and the UV light required to control their psoriasis.

An increasing number of physicians are prescribing the twice weekly application of ultrapotent topical corticosteroids like halobetasol propionate *(Ultravate),* betamethasone dipropionate–augmented *(Diprolene),* clobetasol propionate *(Dermovate, Temovate),* and diflorasone diacetate *(Psoracom)* to reduce the risk of tachyphylaxis

*International Nonproprietary Names (INN) and British Approved Names (BAN)
**US Adopted Names (USAN)

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Treatment Options For Localized Scleroderma

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ABSTRACT

Localized scleroderma, or morphea, is a chronic disease that causes a thickening and induration of the skin. For plaque type morphea, the treatments of choice include super-potent corticosteroids and calcipotriol. For the more generalized forms, as well as the linear forms, UVA is currently the best therapeutic modality. Patients with localized scleroderma are managed by both rheumatologists and dermatologists. There is still much therapeutic uncertainty in this disease.

KEY WORDS: *calcipotriol, corticosteroids, morphea, scleroderma, UVA, PUVA*

Localized scleroderma (LS), or morphea, has been classified into plaque, generalized, linear, and deep forms[1]. The natural progression of the plaque form of LS is of a gradual softening to spontaneous resolution after a mean duration of 4 years with the plaque group having the shortest period of activity and the deep form the longest[2]. Significant disability occurs in both linear and deep forms of morphea. Both the plaque and generalized forms can also be disfiguring, since spontaneous resolution does not invariably occur. To prevent such outcomes, clinicians use topical corticosteroids, antimalarials, etretinate, penicillin, D-penicillamine, phenytoin, vitamin E and griseofulvin. Because none of these have been used in controlled studies, favorable improvement due to spontaneous resolution cannot be excluded[3].

Treatment	Morphea Type	Number of cases	Not improved
Bath PUVA[4,6,10]	P/G L D	13 6 1	2 1 -
Systemic PUVA[7-9,11]	P/G L D	5 3 1	1 1 -
High dose UVA_1 [11]	P/G L	9 1	- -
Low dose UVA_1[5,11,12]	P/G L D	21 14 3	- - 2

Table 1: Compilation of reported cases of morphea treated with UVA light modalities.
Legend: Generalized or plaque type morphea (P/G); linear morphea (L); Deep morphea (D).

Use of Ultraviolet A

Published reports suggest that high dose UVA_1 may be the most efficacious form of light treatment followed in order, by low-dose UVA_1, and UVA in conjunction with topical and systemic psoralens (PUVA) (see Table 1). UVA and UVA_1 treatment have yet to be compared clinically. However, the potential long-term toxicity of long wave UVA is still unknown, and its light sources are not readily available in North America. Further, the long-term oncogenic potential of PUVA is well documented. Given the propensity for skin thickening to improve, double-blind, controlled, randomized studies are needed to confirm the efficacy of these treatment modalities.

Use of vitamin D derivatives

Calcitriol has an antisynthetic and antiproliferative effect on fibroblasts from sclerodermatous skin. Oral calcitriol also has a beneficial effect on localized scleroderma mediated through immune or local effects. Regular monitoring for hypercalcemia and hypercalciuria is required. A serial renal ultrasound may be required to detect potential nephrocalcinosis[13]. Calcipotriol/calcipotriene, a calcitriol analogue, has also been shown to inhibit the growth of fibroblasts from sclerodermatous skin.

Use of Systemic Immunomodulation

Because immune cell activation is believed to underlie the development of skin sclerosis, systemic immunosuppressants have been used to treat severe and refractory localized scleroderma. Methotrexate is a folic acid analogue with multiple anti-inflammatory effects and has been found to be beneficial for treatment of morphea.

Treatment	Morphea type	Numbers treated	Dose and duration	Outcome
Calcitriol[20,,21,27] (Oral)	G D L	2 2 7	0.25 – 1.25 µg OD for 3 – 10.5 months	Improved ↑ urinary calcium 6/7 improved
Calcipotriol[22, 23] (Topical)	P/G and L	12	Nightly occlusion with ointment (0.005%) BID for 3 months	52% improvement in skin score
	L	1	Cream (0.005%) BID for 6 months	50% decrease in surface area

Table 2: Vitamin D derivatives and morphea.

Corticosteroids have been used systemically to treat severe disease. Treatment with antimalarials[15,16], azathioprine[17], sulfasalazine[18], and D-penicillamine[24] has also been described in anecdotal fashion. Use of combination antimalarial therapy, i.e., quinacrine with hydroxychloroquine or chloroquine, can be of benefit in patients with cutaneous lupus refractory to single agent therapy alone[19]. This may be a safe and worthwhile strategy in generalized morphea. These immunosuppressive drugs have potential side-effects and appropriate monitoring is required.

Treatment	Morphea type	Numbers treated	Dose and duration	Outcome	Risks
Corticosteroids[14]	G L	5 12	Prednisone 0.5–1 mg/kg/day, tapered over 14 months	14/17 improved	Osteoporosis, growth arrest, diabetes, hypertension, cataracts, infection
D-penicillamine[24]	G L	3 8	2–5 mg/kg/day, for 15–53 months	7/11 improved	Bone marrow suppression, nephrotic syndrome, autoimmune disease
Antimalarials[15,16,25]	P/G D	4 7	Hydroxychloroquine 200-400 mg OD or chloroquine 250 mg OD, duration not specified	2/4 improved 4/7 improved	Ocular toxicity, bone-marrow suppression, dyspigmentation
Methotrexate[26]	G	9	15mg/wk–25mg/wk for 24 weeks	6 completed, 5/6 improved	Hepatotoxicity, bone marrow suppression, infection

Table 3: Larger case series of morphea patients treated with other medications. Benefits claimed by any of these therapeutic options have been substantiated by proper clinical trials (cited above).

Summary and an approach to treatment

The clinician is faced with considerable uncertainty when choosing a treatment modality for localized scleroderma. Given the benign natural progression of plaque type morphea, treatment with topical modalities such as super-potent corticosteroids or calcipotriol is prudent. Although no studies of the effectiveness of topical corticosteroids in localized morphea have been published, these agents have been shown to be very effective in lichen sclerosus et atrophicus, a clinically associated condition. For the more generalized forms and the linear forms, the use of UVA (either long wave alone or PUVA) is currently the best documented therapeutic modality. In the absence of access to these modalities and in the face of very active inflammatory disease involving deeper structures, oral calciferol or systemic immunosuppression may be contemplated. Recent studies support the use of methotrexate and systemic corticosteroids but controls are lacking. There remains a great amount of therapeutic uncertainty in this disease, and resolution must await the organization and completion of controlled/blinded multicenter therapeutic trials.

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and skin atrophy. Another approach is to use newer topical corticosteroids like mometasone furoate *(Elocom, Elocon)* or fluticasone propionate *(Cutivate),* which may have an improved ratio of anti-inflammatory effect to atrophogenic potential.

Occasionally for use on thick plaques of psoriasis, penetration enhancing agents like salicylic acid or urea are added to topical corticosteroids. Examples of such products include betamethasone dipropionate 0.05%/salicylic acid 2% (*Diprosalic* ointment and lotion), and diflucortolone 21-valerate 0.1%/salicylic acid 3% (*Nerisalic* oily cream). Salicylic acid and urea weaken the hydrogen bonds in keratin, and facilitate penetration of the corticosteroid through the keratin to the dermis[2]. Salicylic acid also blocks UVB light. Patients taking UVB light treatment must apply these preparations consistently or they could increase their risk of under- or overexposure to the UVB therapy[4].

Tar

Tar stings, tar stinks, and tar stains! There is little objective evidence demonstrating that adding tar to a topical corticosteroid adds value. Tar increases costs while reducing the shelf life and cosmetic acceptability of the product. Tar is nonstandard, containing about 10,000 different chemicals, and can be highly variable from batch to batch. In addition, tar can cause photosensitivity. Tar has been used in the past as an adjunct to phototherapy (e.g., Goeckerman treatment). It has been largely displaced in recent years by more predictable and better tolerated topical and systemic agents[5].

Topical PUVA

Psoralen plus UVA light treatment can be administered topically as "bath PUVA". This can be very effective, but there is increased risk of phototoxicity and the topical application of psoralen is much more inconvenient than the systemic use of this medication.

Topical porphyrin derivatives

Light-activated porphyrin derivatives for topical and systemic use in psoriasis and other dermatologic conditions are under development[11].

Conclusion

With growing public reluctance to use systemic medications we can expect topical treatments for psoriasis and other skin conditions to become increasingly important in the future. This trend will be supported by our growing understanding of the pharmacology and physical chemistry of topical medications, of skin physiology and cell biology, and of the psychological and compliance issues which influence the acceptability of various treatment modalities.

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…continued from page 4

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
Photodynamic Therapy	**Aminolevulinic Acid** *Levulan* Photodynamic Therapy DUSA Pharmaceuticals	The US FDA approved *Levulan* PDT in December 1999, for the treatment of actinic keratoses. Schering AG - Berlin and DUSA Pharmaceuticals have entered into an agreement giving Schering AG exclusive marketing and distribution rights in the US, Europe and the rest of the world, except Canada. They are planning to launch this product in the second quarter of 2000.
Anticancer Agents	**G-3139** Genta Inc	bcl-2 antisense compound for use in combination with dacarbazine. It is indicated for treatment of advanced malignant melanoma.
Antibacterial Agents	**Moxifloxacin HCl** *Avelox* Bayer	An advisory committee to the US FDA recommended approval in October 1999, of this quinolone antibiotic for the treatment of uncomplicated skin and skin structure infections, acute sinusitis, acute bacterial exacerbations of chronic bronchitis, and community-acquired pneumonia.
Antifungal Agents	**Ciclopirox** *Loprox* 8% Topical Solution Hoechst-Marion Roussel	The US FDA approved this nail lacquer in December 1999, for the treatment of mild to moderate onychomycosis.
Keratolytic Agents	**5-fluorouracil** *Solex* Dermik Laboratories	An NDA was submitted in October 1999, for a treatment using 5-fluorouracil in Advanced Polymer System's *Microsponge* system. This treatment has demonstrated efficacy in reducing actinic keratoses.
Anticancer Agents	**Allovectin-7** Vical Inc	The US FDA granted orphan drug designation to this drug in October 1999, for the treatment of invasive and metastatic melanoma.

Drug News

Anorectal Preparations	Pivotal Phase III trial results for nitroglycerin ointment *(Anogesic)* were released in November 1999. They fell short of efficacy requirements for treatment of chronic anal fissures. Cellegy Pharmaceuticals plans to analyze the trial data and meet with the US FDA to determine the treatment's future course.
OTC Products	The US FDA issued a final rule in September 1999, that all OTC drug products containing colloidal silver or silver salts have been misbranded and are not recognized as safe and effective, and manufacturers will no longer be able to market them. These products were labelled to treat adults and children for HIV, AIDS, cancer, tuberculosis, malaria, lupus, syphilis, scarlet fever, shingles, herpes, pneumonia, typhoid and tetanus.
HIV and AIDS	Researchers at the National Institute of Allergy and Infectious Diseases hypothesize that HIV may continue to infect CD4+ T-cells after treatment with current HIV drugs. They suggest that current HIV drugs may never eliminate the virus from the body, though treatment can keep the virus levels stable.
Hair Growth	The US FDA's pharmacy compounding committee in November 1999, recommended against including dinitrochlorobenzene (DNCB) and diphenylcyclopropenone (DPCP) on a list of drug substances that can be used in compounding. These substances were used to treat alopecia areata and resistant viral warts.

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