Therapeutic options in the treatment of psoriasis and atopic dermatitis

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A variety of therapeutic options are available to treat psoriasis and atopic dermatitis (AD). Local agents typically are used to treat localized and milder forms of disease, whereas phototherapy and systemic agents are used for more generalized and severe disease. Various combinations and sequences of topical or systemic therapies, or both, have been utilized in the treatment of psoriasis and, less frequently, of AD. Conventional systemic therapies for psoriasis, such as corticosteroids, oral calcineurin inhibitors, antimetabolites, and retinoids, are limited by their propensity to cause serious side effects. More recently, a number of immunobiologic agents, such as monoclonal antibodies, recombinant cytokines, and fusion proteins, have been approved by the Food and Drug Administration or are undergoing development as systemic antipsoriatic treatments. In many of these categories, a number of exciting new therapies are in development that may augment the existing armamentarium available to clinicians for the treatment of inflammatory skin diseases. (J Am Acad Dermatol 2005;53:S3-16.)

A wide variety of therapies are available to treat inflammatory dermatoses such as psoriasis and atopic dermatitis (AD). Topical agents typically are used first for localized and milder forms of these diseases and to control flares of skin disease in patients with widespread or more severe disease. Systemic therapies are reserved for more severe disease because they typically carry a greater risk of significant side effects, particularly with long-term use, although a number of immunobiologics recently introduced for psoriasis hold the promise of high efficacy with reduced side-effect potential. Various combinations and sequences of topical or systemic therapies, or both, have been utilized in the treatment of psoriasis and, less frequently, of AD. This article reviews topical and systemic therapies used to treat psoriasis or AD and discusses agents under development.

Abbreviations used:

AD:	atopic dermatitis
APC:	antigen-presenting cell
FDA:	Food and Drug Administration
ICAM:	intracellular adhesion molecule
IFN-γ:	interferon gamma
Ig:	immunoglobulin
IL:	interleukin
IL-2R:	interleukin 2 receptor
IMP:	inosine monophosphate
LFA:	lymphocyte function-associated antigen
MHC:	major histocompatibility complex
PUVA:	psoralen plus ultraviolet A
TCI:	topical calcineurin inhibitor
TCR:	T-cell receptor
T_H1, T_H2:	T-helper cell, type 1 and type 2
TIG:	tazarotene-induced gene
TNF-α:	tumor necrosis factor alpha
UVA:	ultraviolet A
UVB:	ultraviolet B

TOPICAL AGENTS

In addition to corticosteroids, in the past decade, vitamin D analogues, an anthralin preparation, topical retinoids, and topical calcineurin inhibitors (TCIs) have expanded the clinician's armamentarium.

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Corticosteroids

Topical corticosteroids are the most commonly prescribed treatment for psoriasis in the United States[1] and are frequently used to treat acute exacerbation of AD. They come in various strengths and formulations, which provide clinicians with substantial flexibility in their approach to treatment. The relative strength or potency (which ranges from class 1 or superpotent to class 7 or least potent) of each corticosteroid is based on its ability to produce vasoconstriction and blanching when applied to the skin of healthy volunteers.[2,3] The mechanisms of action of corticosteroids include immunosuppression, anti-inflammation, antiproliferation, and vasoconstriction, which are largely mediated through binding with intracellular corticosteroid receptors and regulation of gene transcription, including regulation of genes coding for cytokines.[4]

Topical corticosteroid treatment of psoriasis and AD is effective, relatively rapid, well tolerated, easy to use, and sometimes less expensive than many alternative therapies. Therapy often begins with daily application of a topical corticosteroid for initial lesion control before switching to twice-weekly administration with a lower potency corticosteroid or to an alternative drug for treatment maintenance.

However, side effects associated with topical corticosteroids, which include atrophy or thinning of the skin, striae, telangiectases, acneiform eruption, rosacea, contact dermatitis, and side effects secondary to systemic absorption, can be troublesome if these agents are used inappropriately or longer than recommended.[5] Mid- or high-potency agents should not be used on the face, intertriginous areas, or in infants or small children, who possess an increased skin surface-to-body mass ratio. Higher potency agents should not be used for more than 2 weeks. Topical corticosteroids are typically not used in patients with psoriasis who have more than 20% of their body surface affected.

Vitamin D_3 analogues (calcipotriene)

Calcipotriene is a vitamin D_3 analogue that is available as a 0.005% cream or ointment to treat plaque psoriasis and as a 0.005% solution for chronic, moderately severe scalp psoriasis.[6-8] Calcipotriene cream and solution should be applied twice daily, whereas calcipotriene ointment may be applied either once or twice daily. Calcipotriene is not used in the treatment of AD. One mechanism of action of calcipotriene involves inhibition of keratinocyte proliferation and stimulation of keratinocyte differentiation.[9,10] These actions are mediated via binding with vitamin D receptors located in the nucleus of keratinocytes.[11] The interaction of calcitriol (the active metabolite of vitamin D_3) and presumably calcipotriene with vitamin D receptors leads to alterations in the transcription of vitamin D–responsive genes, including genes involved in keratinocyte differentiation and proliferation as well as ones involved in cell adhesion and trafficking processes.[11] Topical calcitriol also has been shown to decrease T-cell infiltration and keratinocyte intracellular adhesion molecule–1 (ICAM-1) expression in treated plaques.[12] Calcitriol and calcipotriene also may alter gene transcription by antagonizing the effects of other transcription regulators, such as activator protein 1.[11]

Maximal clinical effectiveness appears to require 6 to 8 weeks of treatment, although a therapeutic response may be observed within 2 weeks of therapy initiation.[13] In addition, on the basis of an extensive review of available data, topical vitamin D_3 analogues (usually calcipotriene) have been shown to be significantly more effective than anthralin, but significantly less effective than potent corticosteroids and, in combination with a potent or very potent corticosteroid, significantly more effective than calcipotriene monotherapy.[14]

The most frequently reported adverse event in controlled clinical trials of calcipotriene cream or ointment was skin irritation, including burning and itching with calcipotriene ointment[6,7]; hence treatment of thin-skinned areas such as the face and groin is not advised. Calcipotriene is about 100 to 200 times less potent than vitamin D_3 in terms of effects on calcium metabolism[15]; doses up to the maximum recommended amount of 100 g/wk (50 μg/g of ointment) have been shown to result in small but clinically unremarkable increases in serum calcium levels and calcium excretion. Because of this, calcipotriene is less likely to disturb calcium metabolism, thus avoiding side effects such as calcium mobilization from bone and the formation of kidney stones typically associated with elevated calcium levels.[9] Dose-dependent decreases in serum parathyroid levels and increases in intestinal calcium absorption and serum and urine calcium levels accompanied by frank hypercalcemia have been reported when topical calcipotriene formulations were used at maximum (100 g/wk) and supramaximum (up to 360 g/wk) levels.[16-19] Therefore monitoring of urine calcium excretion is recommended when calcipotriene is administered to patients with a history of hypercalciuria or renal stone formation and when administered for prolonged periods at doses approaching or exceeding the maximum recommended levels.[18]

Tisocalcitate ointment, a new topical vitamin D analogue (Schering AG Germany, Berlin), is currently in phase 2 clinical development for mild to