

Topical treatment of atopic dermatitis

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Atopic dermatitis is the most common chronic skin disease of young children, but can affect patients of any age [1]. More than 50% of these patients develop asthma and allergies [2]. Atopic dermatitis represents an important first step in the atopic march [3]. Rational topical therapy of atopic dermatitis reflects an appreciation of the complexity of the underlying immunopathogenesis (Fig. 1) [4].

Skin barrier abnormality

Patients with atopic dermatitis have xerotic skin and increased transepidermal water loss [5]. The abnormal skin barrier allows increased antigen absorption, contributing to the cutaneous hyperreactivity characteristic of atopic dermatitis [6,7]. Ceramides are major water-retaining molecules in the extracellular space of the stratum corneum that bind a matrix of structural proteins, providing a barrier function [8]. Lesional and nonlesional skin in patients with atopic dermatitis has been found to be deficient in ceramide content, which results in reduced water-binding capacity, higher transepidermal water loss, and decreased water content [9,10]. This deficiency may contribute to skin colonization by *Staphylococcus aureus*, which also characterizes atopic dermatitis skin [11].

Conventional therapy

Topical therapy should be part of a comprehensive approach that incorporates education of the patient or caregiver, recognition and avoidance of proven

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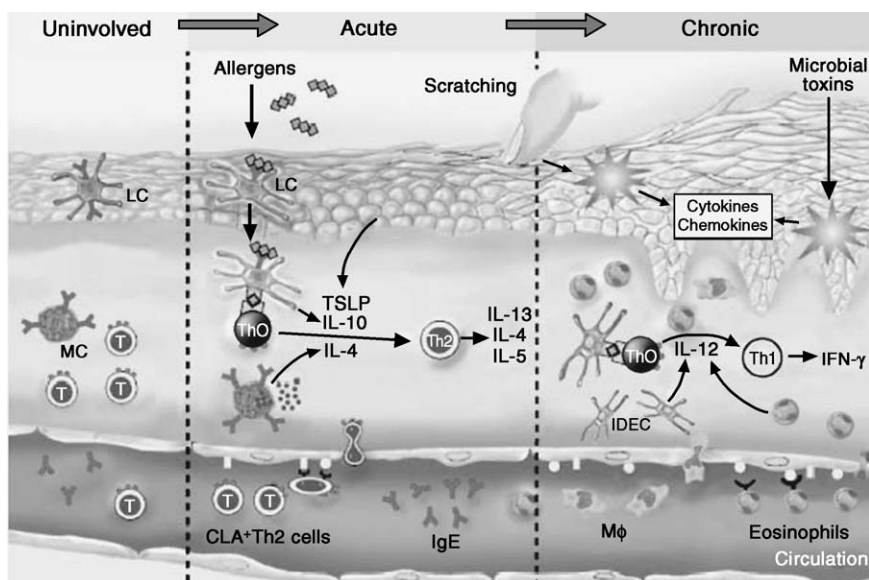


Fig. 1. Immunopathogenesis of atopic dermatitis. CLA⁺, cutaneous lymphocyte associated antigen; IFN-γ, interferon γ; IL, interleukin; MC, mast cell; Th0, T helper cell type 0; Th1, T helper cell type 1; Th2, T helper cell type 2; TSLP, thymic stromal lymphopoietin. (From Leung DYM, Boguniewicz M, Howell M, Nomura I, Hamid Q. New insights into atopic dermatitis. *J Clin Invest* 2004;113:651–7; with permission.)

allergens, hydration, interruption of the itch–scratch cycle, and consideration of the psychosocial aspects of this chronic, relapsing illness [12]. Successful topical therapy includes recognition of what to avoid and what and when to apply. The abnormal stratum corneum that is present even in noninvolved skin contributes to diffusional water loss after application of a topical irritant. Nonspecific and specific triggers may contribute to chronic inflammation in atopic dermatitis. Cleansers with minimal defatting activity and a neutral pH should be used rather than soaps. Skin care products containing alcohol and astringents should be minimized. New clothes should be laundered before use to remove formaldehyde and other chemicals. Liquid detergents are easier to rinse out than powders, and a second rinse cycle may facilitate removal of residual detergent. Rather than counseling patients not to swim in chemically treated pools, patients should be instructed to shower and use a cleanser to help remove chlorine or bromine, followed by application of a moisturizer. Sun exposure can lead to overheating, evaporation, and perspiration, all of which can be irritating. Sunscreens for the face often are best tolerated by patients with atopic dermatitis.

Moisturizers

Use of moisturizers in conjunction with skin hydration may help reestablish and preserve the stratum corneum barrier, reducing susceptibility to irritants [13].

Addition of a moisturizer to topical corticosteroid therapy has been shown to improve clinical outcomes in patients with atopic dermatitis [14,15]. Moisturizers also can decrease the need for topical corticosteroids [16]. Moisturizers are available as ointments (eg, Aquaphor), creams (eg, Vanicream, Cetaphil, Eucerin), lotions, and oils. Although ointments are formulated with the fewest additives and are the most occlusive, they may trap perspiration, resulting in increased pruritus. Lotions and creams may have an irritant effect because of added preservatives or fragrances. Lotions contain more water than creams and may have a drying effect because of evaporation. Although oils can be applied easily, they often prove to be less effective moisturizers. Patients and caregivers should be told to obtain moisturizers in the largest available size (eg, 1-lb or 480-g jars), because moisturizers need to be applied several times each day on a chronic basis. Vegetable shortening can be used as an inexpensive moisturizer, and although petroleum jelly is not a moisturizer, it can be used as a sealer after proper skin hydration.

Because atopic dermatitis is associated with decreased levels of ceramides, a ceramide-dominant emollient (Triceram) was studied in an open-label study as add-on therapy in children with “stubborn-to-recalcitrant” atopic dermatitis [17]. Objective clinical scores improved significantly in 22 of 24 children by 3 weeks, and further improvement occurred in all patients between weeks 6 and 21. Transepidermal water loss decreased concomitantly, and stratum corneum integrity and hydration showed gradual improvement.

α -Hydroxy acids impact keratinization by affecting corneocyte cohesion and stratum corneum formation. They increase dermal mucopolysaccharides and collagen formation. An emulsion of 12% ammonium lactate has been shown to significantly increase the electrical capacitance, skin surface lipids, extensibility, and firmness of the skin and improve skin barrier function [18]. Of potential clinical relevance, 12% ammonium lactate has been shown to mitigate epidermal and dermal atrophy that was induced by topical corticosteroids [19]. Ammonium lactate (Lac-Hydrin) is available in lotion and cream forms and can be applied twice daily, although use on the face, sun-exposed areas, and open lesions should be avoided, as such use results in significant stinging or burning.

Topical corticosteroids

For almost 50 years, topical corticosteroids have been the primary anti-inflammatory therapy for the acute and chronic aspects of atopic dermatitis. They are effective in reducing inflammation and pruritus because they act on multiple resident and infiltrating cells, primarily by inhibiting the transcriptional activity of various proinflammatory genes [20]. Topical corticosteroids may have an effect on bacterial colonization in atopic dermatitis, reducing the density of *S aureus* [21,22].

Topical corticosteroids are available in potencies ranging from extremely high (class 1) to low (class 7) (Table 1) [23]. Usually, a steroid molecule is most potent when it is formulated in an ointment base. Because topical corticosteroids are

Table 1
Representative topical corticosteroid preparations

Group	Preparation
1	Clobetasol propionate (Temovate) 0.05% ointment/cream Betamethasone dipropionate (Diprolene) 0.05% ointment/cream Halobetasol propionate (Ultravate) 0.05% ointment/cream
2	Mometasone furoate (Elocon) 0.1% ointment Halcinonide (Halog) 0.1% cream Fluocinonide (Lidex) 0.05% ointment/cream Desoximetasone (Topicort) 0.25% ointment/cream
3	Fluticasone propionate (Cutivate) 0.005% ointment Halcinonide (Halog) 0.1% ointment Betamethasone valerate (Valisone) 0.1% ointment
4	Mometasone furoate (Elocon) 0.1% cream Triamcinolone acetonide (Kenalog) 0.1% ointment/cream Fluocinolone acetonide (Synalar) 0.025% ointment
5	Fluocinolone acetonide (Synalar) 0.025% cream Hydrocortisone valerate (Westcort) 0.2% ointment
6	Desonide (DesOwen) 0.05% ointment/cream/lotion Alclometasone dipropionate (Aclovate) 0.05% ointment/cream
7	Hydrocortisone (Hytone) 2.5% & 1% ointment/cream

Groups decrease in severity: 1 (super potent) through 7 (least potent).

Adapted from Stoughton RB. Vasoconstrictor assay-specific applications. In: Maibach HI, Surber C, editors. Topical corticosteroids. Basel: Karger; 1992. p. 42–53.

available in a variety of bases, including ointments, creams, lotions, solutions, gels, sprays, foam, oil, and impregnated tape, there is no need to compound these medications. Applying an emollient immediately before using a topical corticosteroid or over a topical corticosteroid-treated area may decrease the effectiveness of the corticosteroid. Ointment-based preparations are most occlusive and have the fewest number of additives. They provide better delivery of the medication and decrease evaporative losses; however, cream formulations may be better tolerated during periods of excessive heat or humidity. Although creams and lotions are easier to apply than the ointments discussed above, they may contribute to skin irritation and xerosis. Solutions are useful on the scalp or other hirsute areas, although their alcohol content can be irritating. The various ingredients that are used to formulate the different bases may be irritating to some patients and may cause sensitization. Rarely, the corticosteroid molecule itself can induce an allergic contact dermatitis [24].

Prescribing the correct topical corticosteroid depends in large part on the severity and distribution of eczematous lesions. Patients and caregivers need to be educated about the potency and potential side effects of the prescribed topical corticosteroid preparations. Patients often erroneously assume that the potency of a topical corticosteroid is defined by the number next to the compound name (eg, 2.5% versus 0.05%). Although using the least-potent, most-effective corticosteroid is typically a good rule to observe, this approach needs to be balanced by the possibility that the initiation of therapy with a weak preparation may result in persistence or worsening of atopic dermatitis, leading to decreased adherence

to the prescribed treatment regimen. A step-wise approach, starting with a mid- or high-potency preparation (except to eczema involving the face, axillae, or groin areas) followed by a lower potency preparation with clinical improvement, may be a more effective strategy. One study of children as young as 3 months found that 0.05% fluticasone propionate cream was safe and effective, even when applied on the face and on significant areas of the body for up to 1 month [25]. Another study suggested that a 3-day course of a potent topical corticosteroid was equivalent in clinical efficacy to chronic use of a low-potency steroid [26]; however, discontinuing use of a high-potency corticosteroid without a step-down plan can result in rebound flaring of the atopic dermatitis. Rarely, resistant lesions may require a potent topical corticosteroid therapy under occlusion, although this approach should be used cautiously and reserved primarily for severe eczema of the hands or feet [27]. Prescribing topical corticosteroids in inadequate amounts also can contribute to suboptimal control of atopic dermatitis. Because approximately 30 g of medication are needed to cover the entire body of the average adult [28], patients with widespread disease who must refill prescriptions frequently may undertreat their eczema or become nonadherent with their prescribed regimen. Obtaining medications in larger quantities can result in significant savings to patients. In children with atopic dermatitis, the fingertip unit (FTU), defined as the amount of topical medication extending from the tip to the first joint on the palmar aspect of the index finger, has been described as a measure for applying topical corticosteroids [29]. It takes approximately 1 FTU to cover the hand or groin, 2 FTU for the face or foot, 3 FTU for an arm, 6 FTU for the leg, and 14 FTU for the trunk.

Patients with atopic dermatitis may not respond appropriately to their prescribed topical corticosteroid. In addition to inadequate potency of the prescribed preparation or insufficient amount dispensed, as discussed earlier, other causes for treatment failure may include *S aureus* superinfection, steroid allergy, and corticosteroid insensitivity [30]. Therapeutic failure of topical corticosteroids also may be the result of nonadherence: A significant number of patients and caregivers admit to nonadherence because of a fear of adverse effects [31].

Emerging therapy with topical corticosteroids

Topical corticosteroids typically are prescribed for twice-daily use, although once-daily use has been shown to be effective for certain corticosteroid preparations, including fluticasone propionate [32] and mometasone furoate [33]. Because chronic treatment with topical corticosteroids can result in adverse effects, such as cutaneous atrophy, such therapy has not been considered appropriate for maintenance therapy, especially with normal-appearing skin. Three studies of fluticasone propionate treatment in patients as young as 3 months have demonstrated that once control of atopic dermatitis has been achieved, long-term control can be maintained with a twice-weekly regimen in which the medication is applied once on each of the 2 days [34–36]. During the main-

tenance phase of these studies, the corticosteroid preparation was applied to previously involved areas that had healed, which resulted in delayed relapses, compared with placebo therapy.

Topical calcineurin inhibitors

Although topical corticosteroids have been the mainstay of drug therapy in atopic dermatitis, alternative therapies with appropriate safety margin and clinical efficacy have been the subject of considerable research. The development of a new class of nonsteroidal topical immunomodulators has been a milestone in the therapy of atopic dermatitis [37]. Topical calcineurin inhibitors were developed after it was found that systemically administered cyclosporin A, which is used to prevent solid-organ rejection, was beneficial in treating concomitant psoriasis [38]. Although cyclosporin A was shown to be useful for treating atopic dermatitis [39], it was found to be ineffective when applied topically because of its large molecular size [40]. Tacrolimus in ointment form [41] and pimecrolimus cream were shown to be effective in treating atopic dermatitis [42]. Tacrolimus and pimecrolimus bind to an intracellular immunophilin (FK-binding protein-12, or macrophilin-12), which is the soluble receptor for the immunosuppressant drug FK506. This complex inhibits the phosphorylase activity of calcineurin, a calcium ion-calmodulin-dependent protein phosphatase that is involved in the dephosphorylation of the nuclear factor of activated T cells, a transcription factor for a number of T helper type 1 and 2 inflammatory cytokines (Fig. 2) [43]. In the skin of patients with atopic dermatitis, a number of resident and infiltrating cells, including keratinocytes, Langerhans cells, mast cells, and eosinophils, have FK-binding protein-12 and down-regulate their mediator release or cytokine expression after treatment with tacrolimus and pimecrolimus [44,45].

Clinical trials with tacrolimus ointment

Ointment with 0.03% and 0.1% tacrolimus has been shown to be safe and effective in the treatment of adults and children aged 2 years or older with atopic dermatitis. Clinical trials have included more than 13,000 patients worldwide, and safety and efficacy data are available for up to 4 years of tacrolimus therapy [42]. The first controlled, multicenter, phase II trials conducted in the United States in children [46] and in Europe in adults with moderate-to-severe atopic dermatitis documented the safety and efficacy of treatment with tacrolimus ointment [47]. In phase III, vehicle-controlled trials involving adults and children with moderate-to-severe atopic dermatitis who were treated with 0.03% and 0.1% tacrolimus ointment, up to 41% of ointment-treated patients had at least 90% clearing at 12 weeks, compared with 7% of vehicle-treated patients [48–50]. Use of topical corticosteroids was not allowed during these studies. Blood levels of tacrolimus were undetectable in 80% to 90% of the samples in the adult and pediatric studies, respectively, and no clinically relevant adverse events were

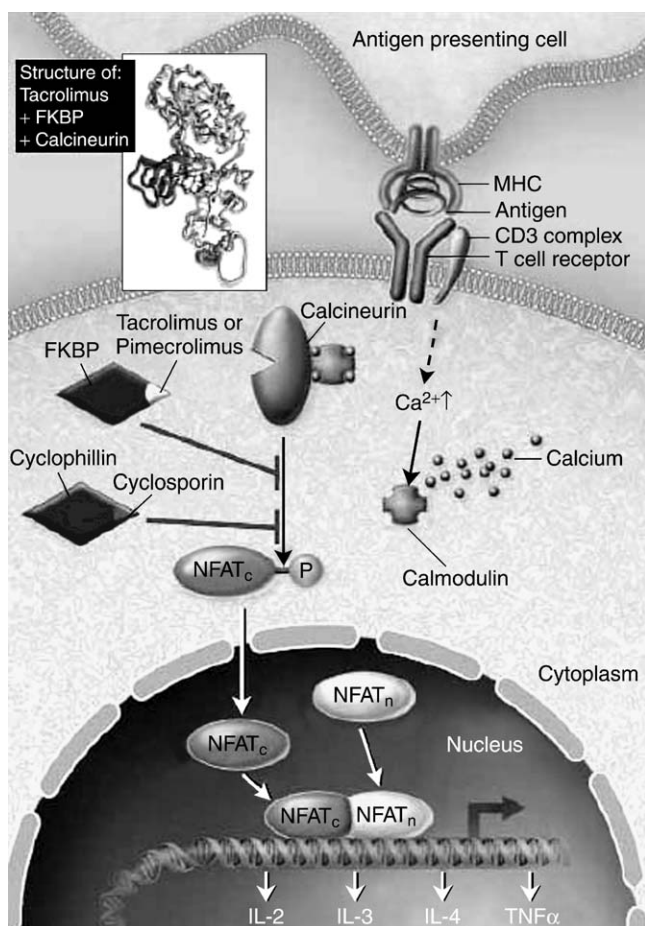


Fig. 2. Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, block transcription of inflammatory cytokines. FKBP, FK-binding protein; MHC, major histocompatibility complex; NFAT, nuclear factor of activated T cells; $\text{TNF}\alpha$, tumor necrosis factor α . (From Nghiem P, Pearson G, Langley RG. Tacrolimus and pimecrolimus: from clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis. *J Am Acad Dermatol* 2002;46:230; with permission.)

noted in patients with detectable levels or drug accumulation. In adults, but not children, a dose–response effect was seen between the 0.03% and 0.1% strengths of tacrolimus ointment, particularly in patients with severe skin disease. A local burning sensation and pruritus were the only common adverse events and tended to diminish with continued application. In long-term (up to 12 months), open-label studies involving adults and children, application of tacrolimus ointment on up to 100% of body surface area demonstrated sustained efficacy and no significant side effects [51,52]. No tachyphylaxis was observed over the course of the year-long therapy in the adult trial, and delayed-type hypersensitivity testing was not affected with this monotherapy [51]. In the multicenter, pediatric study,

0.1% tacrolimus ointment was applied twice daily for up to 1 year in patients with moderate-to-severe atopic dermatitis [52]. The mean eczema area and severity index score showed a 61% improvement from baseline after 3 months of treatment and a 71% improvement after 1 year. Pruritus decreased throughout the trial, and application site burning tended to diminish after the first few days of tacrolimus use. Use on the face, including the eyelids, was well tolerated. An earlier study had confirmed that tacrolimus had no potential to cause cutaneous atrophy [53]. During long-term treatment with tacrolimus ointment, *S aureus* colonization decreased, and no increase in cutaneous infection rates were observed [54,55]. The clinical improvement in patients treated with tacrolimus ointment was associated with significant improvement in quality of life [56]. Currently, tacrolimus ointment is approved by the Food and Drug Administration (FDA) as Protopic 0.03% for children aged 2 to 15 years and 0.03% and 0.1% for adults for short-term and intermittent long-term use in moderate-to-severe atopic dermatitis. Use of sunscreen is recommended as a precaution, although long-term surveillance has not shown any increase in skin cancer.

Clinical trials with pimecrolimus cream

Pimecrolimus, an ascomycin derivative, was found to be effective in treating inflammatory skin conditions, including atopic dermatitis [42,57]. The 1% concentration of pimecrolimus cream was determined to be the most effective concentration for treating atopic dermatitis [58]. Topical 1% pimecrolimus cream was shown to have little systemic absorption in children and adults with atopic dermatitis. In a study of 22 children aged 3 to 23 months, investigators measured the systemic availability of topical 1% pimecrolimus cream applied twice daily for 3 weeks to all affected areas, including the face and neck [59]. The percentage of involved body surface area ranged from 10% to 92%. Pimecrolimus blood concentrations were consistently low; approximately one third of the samples were below the assay's limit of quantitation, and 98% of the samples had concentrations of less than 2 ng/mL. Long-term pharmacokinetic studies with repeated application of pimecrolimus did not show any significant drug accumulation.

Investigators pooled results from two identical multicenter, double-blinded, randomized, vehicle-controlled studies of 1% pimecrolimus cream applied twice daily for 6 weeks in children aged 2 to 18 years with mild-to-moderate atopic dermatitis. By 6 weeks, 34.8% of pimecrolimus-treated patients were clear, compared with 18.4% of vehicle-treated children ($P \leq 0.05$) [60]. A low rate of burning and stinging, similar to that seen in vehicle recipients, was reported in pimecrolimus recipients. Although 1% pimecrolimus cream is not approved by the FDA for use in children younger than 2 years, several studies have shown this treatment to be well tolerated and effective in infants with atopic dermatitis [61,62]. The treatment is FDA approved for use in children and adults with mild-to-moderate atopic dermatitis.

New directions in topical therapy

Topical calcineurin inhibitors have been compared with topical corticosteroids in a limited numbers of studies. Compared with a mid-potency corticosteroid, 0.1% tacrolimus ointment was shown to be similar in efficacy in adults with moderate-to-severe atopic dermatitis [63]. Compared with a low-potency corticosteroid, 0.03% and 0.1% tacrolimus ointments were shown to be more effective in children with moderate-to-severe atopic dermatitis [64]. Results from a multicenter European trial showed that 0.03% tacrolimus applied twice or once daily in children with moderate-to-severe atopic dermatitis was more effective than twice-daily treatment with 1% hydrocortisone acetate ointment [65]. These results are not surprising, as the choice of 1% hydrocortisone acetate for patients (including children) with moderate-to-severe atopic dermatitis would not be expected to result in clinical improvement. In noncomparative studies, patients who had moderate-to-severe atopic dermatitis despite treatment with topical corticosteroids often responded dramatically to tacrolimus ointment monotherapy [51]. Reitamo et al [65] showed that although the twice-daily regimen with lower-strength tacrolimus was more effective in patients with severe atopic dermatitis, the once-daily regimen was sufficient for patients with moderate disease. Rather than considering topical calcineurin inhibitors in opposition to topical corticosteroids, a more useful clinical approach would be considering the two classes of drugs in a complementary manner, taking advantages of the unique aspects of each class. The optimal combination has yet to be defined. Several studies incorporating a novel approach are discussed.

Given the chronic and relapsing nature of atopic dermatitis, the question of whether treatment of early signs or symptoms of disease with a topical calcineurin inhibitor could influence long-term outcomes by preventing disease progression is of great practical importance to clinicians. This issue was addressed in long-term trials (up to 1 year in duration) in infants, children, and adults treated with 1% pimecrolimus cream [62,66,67]. The primary efficacy parameter was the incidence of flares and need for topical corticosteroid rescue. In the infant study, 64% of pimecrolimus recipients, compared with 35% of vehicle recipients, did not require topical corticosteroid use during the study [62]. Subgroup analysis showed that significantly fewer flares occurred in pimecrolimus-treated children with disease of all clinical severities (eg, mild, moderate, severe) [66]. In adults treated for 24 weeks, 45% in the pimecrolimus-treated group did not experience any flares, compared with 19% in the control group. Topical corticosteroids were used on 14% of the days in the pimecrolimus-treated group and on 37% of the days in the control group [67]. The median time to first flare was 144 days in the pimecrolimus-treated group and 26 days in the control group. These studies suggest that earlier use of a topical calcineurin inhibitor can lead to better long-term disease control with fewer flares and significantly lower need for topical corticosteroid rescue therapy. They also support a shift in the treatment paradigm—using topical calcineurin inhibitors as first-line therapy and using topical corticosteroids as rescue therapy (Fig. 3) [68].

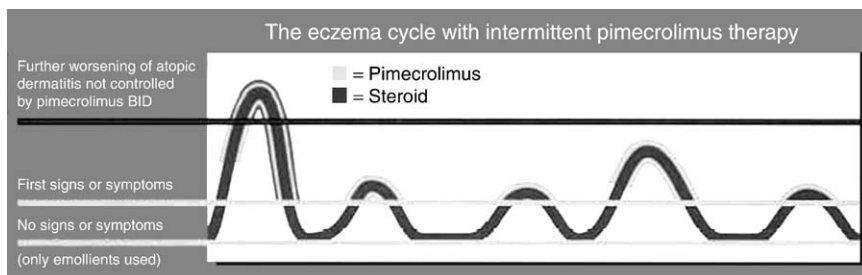


Fig. 3. Early intervention strategy with a topical calcineurin inhibitor using topical steroid as rescue therapy. BID, twice daily. (From Boguniewicz M, Eichenfield LF, Hultsch T. Current management of atopic dermatitis and interruption of the atopic march. *J Allergy Clin Immunol* 2003;112:S146; with permission.)

This change would be especially appropriate for treating eczematous rash involving the face, groin, or axillae and may make cost-effective sense in subgroups of patients [69]. A new practice parameter for management of atopic dermatitis incorporates this novel therapeutic approach [70]. Studies are underway to determine if using early intervention with a topical calcineurin inhibitor and a topical corticosteroid as rescue therapy soon after diagnosis of atopic dermatitis can impact the natural history of the skin disease and interrupt the atopic march.

Summary

Atopic dermatitis is a common chronic skin disease that is often the first step in the atopic march. Significant insights have been gained in the understanding of the complex immunopathogenesis of this disease. A new class of topical immunomodulators, the calcineurin inhibitors, has been shown to be safe and effective in children and adults with atopic dermatitis. New treatment strategies are emerging and will be incorporated into an updated practice parameter. Ongoing studies are evaluating the impact of early intervention with a topical calcineurin inhibitor on the atopic march.

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