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CLINICAL UPDATE

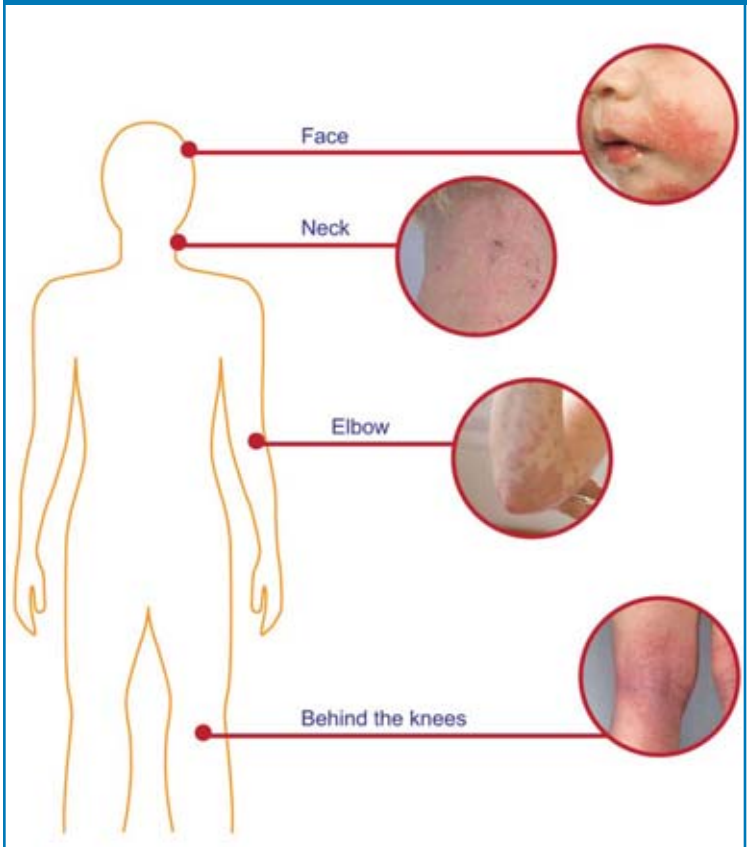
The Treatment of Atopic Dermatitis

INTRODUCTION

Atopic dermatitis (AD) is a common chronic skin disorder characterized by recurrent episodes of pruritus, eczematous lesions, xerosis (dry skin), and lichenification (**Figure 1**).[1] Although it may be perceived as a minor skin condition, AD is, in fact, a serious disorder that sometimes requires hospitalization and that has a substantial adverse impact on sleeping patterns, emotional well-being, productivity, and psychosocial functioning.[1-5] It is associated with other atopic diseases such as asthma and allergic rhinitis,[1,6] as well as burdensome and serious comorbidities such as secondary bacterial and viral infections.[1] In the United States, AD affects an estimated 10% to 20% of children, and 1% to 3% of adults. Approximately 60% of patients develop symptoms by 1 year of age, and 85% by age 5. It is the most common childhood dermatologic disorder.[1,7]

The complete pathophysiology of AD has not been elucidated, but contemporary research suggests that AD is the result of interactions among genetic, immune, infectious, environmental, and other factors that result in the characteristic, recurring, and intensely pruritic, erythematous, and inflamed eczematous lesions. Lesions of AD most commonly occur on sensitive areas of skin such as the face, neck, and skin folds (behind the knees and elbows), making treatment with some powerful topical agents challenging.[1,2]

FIGURE 1. Patient AD Triggers[1]



Source: Krakowski et al.[1]

See Important Safety Information and accompanying Prescribing Information on page 6 for Elidel®.

The cycle of exacerbation and remission that typifies AD recurs frequently over the course of patients' childhood and adult life. A survey of 2,002 patients and caregivers of children with moderate to severe AD found that patients average nine AD flares each year and that each flare lasts approximately 15 days, for an average of approximately 135 days of each year spent in flare.[2] Patients reported that flares had a substantial impact on their daily lives, with 86% of patients reporting that they avoid at least one normal everyday activity during a flare and others reporting that flares adversely affected their school, home, and social lives.[2]

Successful management of AD requires long-term lifestyle changes and trigger avoidance, as well as long-term pharmacologic treatment. The two main goals of AD management are to heal the skin and to reduce the incidence of flares while increasing the time between flares. Topical corticosteroids are considered the first-line treatment for the acute management of pediatric and adult AD flares, but the long-term use of these agents is limited by their tolerability and safety profiles.[1,8] Topical calcineurin inhibitors (TCIs; tacrolimus and pimecrolimus) are approved by the US Food and Drug Administration (FDA) for the short-term and noncontinuous chronic treatment of AD and are an alternative for ongoing therapy of AD flares. This article reviews the role of TCIs, specifically pimecrolimus cream 1% (Elidel®), in the management of mild to moderate AD in adults and children 2 years of age or older.

TABLE 1. Patient AD Triggers[1]

Associated with direct contact
- Toiletries containing alcohol, astringents, or fragrances
- Hard detergents/soaps
- Abrasive clothing (wool or synthetics)

Associated with physiologic/emotional stressors
- Infections (eg, especially from Staphylococcus aureus, viruses, fungi)
- Overheating/sweating
- Low-humidity environment
- Psychological stress

Associated with food (rarely)
- Food allergens found in:
  - ~ Cow's milk
  - ~ Eggs
  - ~ Peanuts
  - ~ Tree nuts (walnuts, cashews)
  - ~ Soy
  - ~ Wheat
  - ~ Fish
  - ~ Shellfish

Source: Adapted from Krakowski et al.[1]

NONPHARMACOLOGIC MANAGEMENT OF AD

The nonpharmacologic management of AD requires identifying and avoiding known flare triggers and irritants such as detergents, foods, and stress (**Table 1**)[1] and helping patients develop and adhere to good skin care routines. Skin care is a cornerstone of AD management and may include emollients, moisturizers, hydro gels, and ceramide-containing products that reduce and control xerosis and restore skin barrier function. There are few data on specific products, and guidelines do not specifically recommended individual products.[1,8] In general, patients should use dye- and fragrance-free products of their choosing. Patient preferences are important considerations in the selection of skin care products, as patients are more likely to use products that they choose and like. Also important to the success of nonpharmacologic management are patient education and ensuring that patients know and understand their triggers and how to avoid them, as well as how to select and use skin care products.

PHARMACOLOGIC MANAGEMENT OF AD

Avoiding triggers and adopting good skin care practices will help control AD; however, flares requiring over-the-counter (OTC) and/or prescription medication will inevitably occur. Available AD pharmacologic therapies in some patients include topical OTC and prescription corticosteroids, TCIs such as pimecrolimus cream 1%, and adjunctive medications. Adjunctive medications may include systemic corticosteroids and immunosuppressants for severe disease, oral and/or topical anti-infective agents for concomitant infections, and antihistamines for sedation and restoration of normal sleeping patterns.

Topical Corticosteroids

Topical corticosteroids are the first-line treatment for the acute management of AD flares. Multiple agents with variable vehicles and potency are available and prescribed according to disease severity and physician and patient preferences.[8] As a class, topical corticosteroids have anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive properties that effectively control AD flares. However, these agents are also associated with a variety of side effects that limit long-term chronic use. Local adverse effects include skin atrophy, striae, telangiectasias, hypopigmentation, rosacea, perioral dermatitis, acne, cataracts, and glaucoma. Local adverse events may be more common in the treatment of sensitive areas of the skin such as those often affected in AD. There are also reports of systemic side effects, including suppression of the hypothalamic-pituitary-adrenal axis, growth retardation, and reduced bone density.[1] Because of these risks, other treatments that provide maintenance therapy of an AD flare once it is acutely controlled with a topical corticosteroid are desirable.

TCIs—Pimecrolimus

Pimecrolimus cream 1% (Elidel®) is indicated as a second-line therapy for the short-term and noncontinuous chronic treatment of mild to moderate AD in immunocompetent adults and children 2 years of age or older who have failed to respond adequately to other topical prescription treatments or when those are not advisable. Pimecrolimus cream 1% is very effective when it is used at the first signs or symptoms of a flare through resolution, thereby decreasing the likelihood of a full-blown outbreak and possibly limiting overexposure to topical corticosteroids.

TABLE 2. Epidemiologic Studies Reporting No Increased Risk of Malignancies Associated With TCI Use[10-15]

Study	Design	Outcome of Interest	Key Results (related to Elidel®)
Margolis DJ et al. *Dermatology.* 2007; 214:289-295.[10]	Case-controlled study using questionnaire mailed to 5,000 adults with dermatitis; 70.7% responded, and 25.7% reported TCI exposure (Elidel® patients=471)	NMSC	No increased risk of NMSC
Hui RL et al. *Ann Pharmacother.* 2009;43:1956-1963.[11]	Retrospective observational study of 953,064 patients with diagnoses of AD or eczema enrolled in Kaiser Permanente California database between 2001 and 2004 (Elidel® patients=22,716)	Overall cancer and cancer subtypes treated with pimecrolimus	No increased risk of any cancer among patients
Schneeweiss S et al. *Dermatology.* 2009; 219:7-21.[12]	Cohort study of health insurance claims data of initiators of topical pimecrolimus, tacrolimus, and corticosteroids, and patients with untreated dermatitis (N=1,200,645; Elidel® patients=118,863)	Lymphoma	No increased risk of lymphoma among initiators of topical pimecrolimus
Arellano FM et al. *J Allergy Clin Immunol.* 2009;123:1111-1116.[13]	Nested case-controlled study of United Kingdom–based database; 2,738 cases of lymphoma	Risk of lymphoma associated with AD and/or topical corticosteroid (TCS) or TCI use	AD and TCSs associated with increased risk; no association between TCIs and lymphoma; exposure to Elidel® too low for meaningful conclusions
Arellano FM et al. *J Invest Dermatol.* 2007; 127:808-816.[14]	Nested case-controlled study of 294 cases of lymphoma	Lymphoma among patients treated with TCIs	No increased risk
Tennis P et al. *Br J Dermatol.* 2011;165:465-473.[15]	Literature review to assess associations between AD and TCIs with lymphoma, melanoma, basal cell carcinoma, and squamous cell carcinoma	Frequency of malignancy	No increased risk of malignancy associated with TCI use

In 2006, the FDA added a boxed warning to the prescribing information of the TCI class, including pimecrolimus cream 1%, stating that the long-term safety of TCIs has not been established. Although no causal link has been established between the use of TCIs and malignancy, rare cases of malignancy have been reported in patients treated with a TCI.[9]

New Long-Term Data

Numerous epidemiologic investigations have reported the lack of an association between pimecrolimus cream 1% (specifically Elidel®) and an increased risk of cancer. (See **Table 2** for various studies that look at the association of cancer with the use of Elidel®.)[10-15] The long-term safety of pimecrolimus cream 1% is also the subject of the ongoing Pediatric Eczema Elective Registry (PEER), which started in 2004 and is a 10-year observational registry of pediatric patients (ages 2 to 17 years) with AD who have used pimecrolimus cream 1%. The ongoing Surveillance Epidemiology and End Results database will provide comparator data for the incidence of systemic cancers in the general population. As of September 2011, more than 6,000 patients were enrolled and more than 16,000 patient-years of follow-up have been accumulated. The information to date has not demonstrated a signal indicating an increased risk of cancer associated with the use of Elidel®.

Mechanism of Action

Although the mechanism of action is unknown, pimecrolimus has anti-inflammatory activity, which is thought to be the result of calcineurin pathway inhibition. Pimecrolimus binds with high affinity to macrophilin-12, an intracellular protein. The pimecrolimus-macrophilin complex inhibits the enzyme calcineurin, resulting in the suppression of cytokine transcription and T-cell activation. Pimecrolimus also appears to inhibit the production of tumor necrosis factor-α and the release of mediators of inflammation such as histamine. Unlike corticosteroids, which decrease the number of dendritic and Langerhans cells, pimecrolimus has not been shown to affect dendritic cells, B cells, fibroblasts, or other cells.[9,16]

Efficacy

The efficacy of pimecrolimus cream 1% in the management of pediatric and adult patients with mild and moderate AD has been demonstrated in multiple clinical trials. As compared to vehicle, pimecrolimus cream 1% is associated with significant reductions in affected body surface area and erythema, as well as decreases in pruritus, the need for and exposure to corticosteroids, and number of office visits.[17-21] Treatment with pimecrolimus prolongs disease-free periods—time between flares when compared to vehicle—and gives patients and caregivers more relief from the disease.[17,22] It is effective in children (2 years of age or older) and adults intolerant to topical corticosteroids, in sensitive areas of the skin such as the face and neck, and across racial and ethnic groups.[23-26]

One pivotal clinical trial randomized 62 adult patients with moderate AD to pimecrolimus cream 1% (Elidel®) and 68 patients to vehicle to be used at the first signs and symptoms of AD, as needed, over the course of 6 months.[17] Patients in both groups were allowed to

use a moderately potent topical corticosteroid (prednicarbate cream 0.25%) to treat flares.

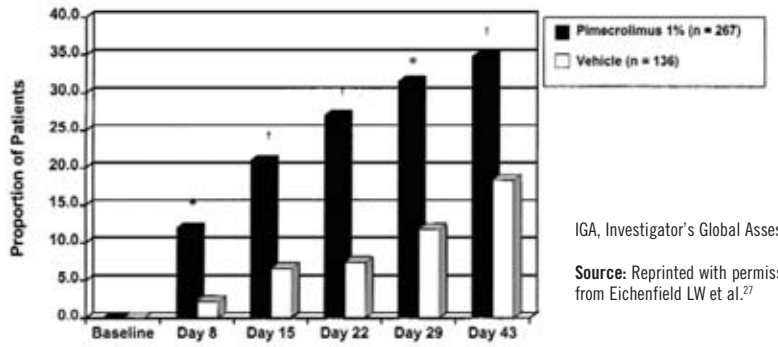
Within 72 hours of treatment, significantly more pimecrolimus-treated patients reported a pruritus score of 0 or 1 ($P<0.01$) than did patients in the vehicle group. This improvement persisted at 24-week follow-up, with 69% of pimecrolimus-treated patients and 35% of vehicle-treated patients reporting pruritus scores of 0 or 1. Major flares—those requiring the use of a topical corticosteroid—were significantly fewer among pimecrolimus-treated patients ($P=0.001$) **(Figure 2)** as was the mean number of major flares among those who suffered one (1 vs 2.3, respectively; $P<0.001$). Consequently, the reliance on and use of the corticosteroid was significantly lower among patients treated with pimecrolimus cream 1% (9.7% vs 37.8% of days during the 6-month study period, $P<0.001$).[17]

Two independent 6-week studies compared pimecrolimus cream 1% with vehicle in 403 pediatric patients between the ages of 1 and 12 years (mean, 6.7 years) with mild to severe disease graded according to the Investigator's Global Assessment (IGA) score (0=clear to 5=very severe disease).[27] Results were pooled for analysis. Approximately 90% of patients in both treatment arms had mild to moderate disease at baseline.

At every follow-up time point during the 6-week studies, pimecrolimus cream 1% was associated with significantly lower IGA scores **(Figure 3)**. At the final visit, 34.8% of pimecrolimus-treated patients were scored as clear or almost clear versus 18.4% of vehicle-treated patients ($P\leq0.05$). Efficacy based on the Eczema Area and Severity Index (EASI) was also better with pimecrolimus cream 1%, particularly in the head and neck region, where a 45% improvement was observed with pimecrolimus cream 1% and no improvement was observed with vehicle at 6 weeks ($P\leq0.001$).[27]

These studies, as well as many others, demonstrate that pimecrolimus cream 1% effectively controls AD flares, prolongs the time interval between flares, and improves symptoms.[17-26]

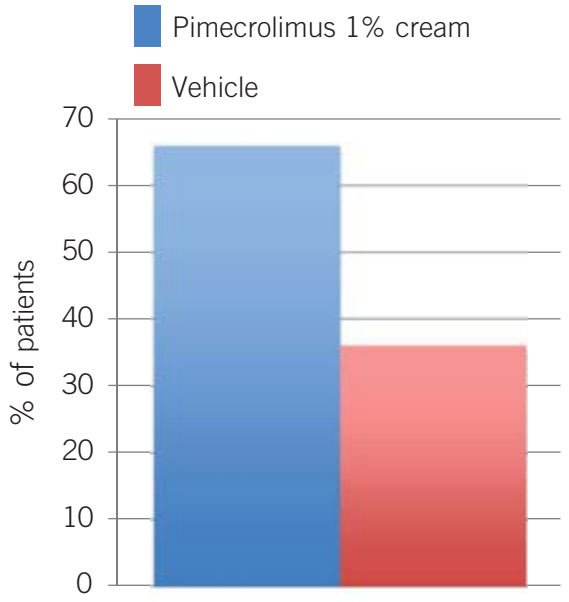
FIGURE 3. Proportion of Patients Clear or Almost Clear Based on IGA Score (0=clear; 1=almost clear) *$P\leq0.05$; †$P\leq0.001$[27]



IGA, Investigator's Global Assessment.

Source: Reprinted with permission from Eichenfield LW et al.[27]

FIGURE 2. Major AD Flares Requiring Topical Corticosteroid Use Among Adults With Moderate Disease After 6 Months[17]



Source: Meurer M et al.[17]

Safety and Tolerability

In clinical trials, the most common local adverse event with pimecrolimus cream 1% in adult and pediatric patients was application-site burning, which occurred in 8% to 26% of patients.[9] Application-site burning tended to be mild to moderate and transient and occurred early in treatment. Other common adverse events include headache, nasopharyngitis, cough, influenza, pyrexia, and viral infection.[9] None of these adverse effects showed an incidence significantly higher than in patients treated with the vehicle alone. Systemic absorption among adults and children is exceeding minimal and below the threshold where systemic complications would be expected.[9,28] Overall, pimecrolimus cream 1% is considered safe and well tolerated in patients with AD 2 years of age or older.

Elidel® Cream should not be the first prescription treatment that you try to treat atopic dermatitis. Prescribe Elidel® Cream only after other prescription treatments did not work or if other prescription treatments are not appropriate.

CONCLUSION

AD is a chronic, recurring, and potentially disruptive and debilitating dermatologic condition. Successful management is a multistep process, requiring successful trigger avoidance, routine skin care, and pharmacologic treatments. Pimecrolimus cream 1% decreases flare incidence, prolongs the duration of time between flares, reduces

symptoms, and effectively treats AD in sensitive skin. It is a safe and effective alternative to corticosteroids for short-term, non-continuous maintenance treatment of pediatric and adult patients with AD where patients have failed to respond adequately to other topical prescription treatment, or where those treatments are not advisable.

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INDICATION AND IMPORTANT SAFETY INFORMATION

ELIDEL® (pimecrolimus) Cream 1% is indicated as second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.

WARNING:

Long-term Safety of Topical Calcineurin Inhibitors Has Not Been Established. Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including ELIDEL Cream.

Therefore:

- Continuous long-term use of topical calcineurin inhibitors, including ELIDEL Cream, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis.
- ELIDEL Cream is not indicated for use in children less than 2 years of age.

ELIDEL® (pimecrolimus) Cream 1% is contraindicated in individuals with a history of hypersensitivity to pimecrolimus or any of the components of the cream.

Patients should be reevaluated if symptoms persist beyond 6 weeks or worsen at any time. Treatment should be discontinued upon resolution of symptoms. Safety of Elidel® cream has not been established beyond one year of non-continuous use. Application should be limited to areas of involvement with atopic dermatitis.

The most common adverse events seen in clinical studies included application-site burning, headache, pharyngitis, nasopharyngitis, cough, influenza, pyrexia, and viral infection. The most common local adverse event seen in clinical studies was application-site burning, which occurred in 8% to 26% of patients treated with ELIDEL Cream. In clinical studies, skin papillomas or warts were observed in 1% of ELIDEL patients.

If patients have lymphadenopathy that is unresolved or of unclear etiology, discontinuation should be considered.

ELIDEL should not be used with occlusive dressings. ELIDEL should not be applied to areas of active cutaneous infections. Patients should minimize or avoid natural or artificial sunlight exposure, even while ELIDEL Cream is not on the skin.