

New Strategies in the Management of Inflammatory Skin Diseases



Clinical Presentation and Pathophysiology of Atopic Dermatitis

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Practical Treatments for Atopic Dermatitis

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Corticosteroid-Free Topical Therapy in the Management of Atopic Dermatitis

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Potential Oral Treatment for Psoriasis and Atopic Dermatitis

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Target Audience

This activity has been developed for dermatologists and other health care professionals involved in the treatment of atopic dermatitis and related inflammatory skin diseases in adult and pediatric populations.

Educational Needs

Atopic dermatitis is a chronic inflammatory skin disease with significant costs and morbidity to patients and their families. Prevalence has been increasing in recent decades, and atopic dermatitis is now estimated to affect more than 10% of children. Atopic dermatitis frequently predates development of asthma and allergic rhinitis in later childhood, and health professionals should be aware of the characteristics that these conditions share. Physicians need to be able to distinguish atopic dermatitis from other eczematous skin conditions, especially in light of the fact that the disease is a contraindication for smallpox vaccination. Because traditional treatment regimens for atopic dermatitis that center on topical corticosteroids have limitations, dermatologists need to keep abreast of evolving alternative therapies such as the new macrolide immunosuppressants tacrolimus and pimecrolimus. These steroid-free products represent a new approach to treating this complex and difficult disease. Health professionals need to understand the mechanisms of action of these novel agents and be cognizant of the findings of recent clinical studies involving topical and oral formulations of the drugs to treat atopic dermatitis and another inflammatory skin disease, psoriasis.

Learning Objectives

By reading and studying this supplement, participants should be able to:

- Summarize revised diagnostic criteria for atopic dermatitis and how these diagnostic guidelines differ from the classic Hanifin-Rajka criteria.
- List several epidemiologic parallels between atopic dermatitis and asthma that have been highlighted in the scientific literature.
- Explain how atopic dermatitis treatment guidelines might be modeled after the three-tiered approach used for asthma care.
- List the chief components of traditional atopic dermatitis therapy and the benefits and limitations of each type of therapy.
- Summarize the findings of short- and long-term, double-blind, controlled clinical studies of topical pimecrolimus in pediatric and adult populations.
- Discuss the findings of recent studies using oral pimecrolimus to treat psoriasis and atopic dermatitis.

Faculty Disclosure

Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. They must also disclose any discussion of investigational or unlabeled uses of products.

Dr. Belsito has received clinical grants from, and is a consultant to, Novartis Pharmaceuticals Corporation and Fujisawa Healthcare, Inc.

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Dr. Tharp has received clinical grants from Biogen, Novartis, Aventis, and Fujisawa, and is a consultant to Biogen, Novartis, and 3M Pharmaceuticals. He discusses the investigational use of leukotrine inhibitors for treating atopic dermatitis.

Clinical Presentation and Pathophysiology of Atopic Dermatitis

Lawrence F. Eichenfield, MD

Atopic dermatitis has been shown to be increasing in prevalence in industrialized countries since World War II, and the condition is now estimated to affect more than 10% of children sometime during childhood.¹

Experienced dermatologists can usually distinguish atopic dermatitis from other types of dermatitis. However, the differences may not be so obvious to the nonspecialist. Distinguishing atopic dermatitis from similarly appearing eczematous skin conditions such as contact dermatitis has recently achieved a new level of urgency and relevance because atopic dermatitis is a contraindication for smallpox vaccination.

Diagnostic Criteria Revisited

For more than two decades, the Hanifin-Rajka criteria have been used to define atopic dermatitis.² Diagnosis using these classic criteria is based on a patient having three or more basic features and at least three minor features from a list of more than a dozen. The basic features are: (1) pruritus, (2) a typical morphology and distribution—facial and extensor involvement in infants and children, flexural lichenification or linearity in adults, (3) chronic or chronically relapsing dermatitis, and (4) personal or family history of atopy (asthma, allergic rhinitis, or atopic dermatitis).

The American Academy of Dermatology (AAD) held a consensus conference on pediatric atopic dermatitis in which Hanifin et al reviewed and updated the classic criteria to help facilitate recognition of the disease by nondermatologists. The conference participants came up with the following simplified diagnostic criteria for atopic dermatitis.

Essential Features

These features must be present for a diagnosis of atopic dermatitis:

- Pruritus
- Eczema (acute, subacute, chronic)
 - Typical morphology and age-specific patterns (including facial, neck, and extensor involvement in infants and children; current or prior flexural lesions in any age group; sparing of groin and axillary regions)
 - Chronic or relapsing history

“Atopic dermatitis has a complex immunology, which is one reason why it is so difficult to manage, particularly in patients with severe disease.”

Important Features

These features are seen in most cases and add support to the diagnosis:

- Early age of onset
- Atopy (personal and/or family history)
- Serum immunoglobulin E (IgE) reactivity
- Xerosis

Most of the other classic secondary features of the Hanifin-Rajka diagnosis, such as keratosis pilaris, facial pallor, and ocular changes, were de-emphasized by the AAD consensus conference and termed “associated features” that help suggest diagnosis but are too nonspecific to define or detect atopic dermatitis for epidemiologic purposes.

Understanding the Pathogenesis of Atopic Dermatitis

Atopic dermatitis has a complex immunology, which is one reason why it is so difficult to manage, particularly in patients with severe disease. Unraveling the complex immunology will enable researchers to better understand why there is such variability in patient disease activity, why atopic dermatitis has strong associations with other atopic conditions, and why the disease is increasing in prevalence. Increased understanding of the mechanisms involved will in turn lead to new therapeutic interventions.

Research on the pathogenesis of atopic dermatitis has come up with some interesting immunologic findings that characterize most patients with the disease, including increased IgE synthesis, excessive T-cell activation in response to an antigen, abnor-

Table 1. Western Lifestyle, Urbanization, and Increasing Prevalence of Atopic Dermatitis

- Increasing prevalence over the past 30 years in industrialized Western countries
- Prevalence higher in immigrants to Western countries than in native lands
- Prevalence higher in industrialized countries with a market economy
- Prevalence higher in urban than in rural areas
- Prevalence higher in privileged socioeconomic groups and smaller families
- Increase most obvious in children and young adults
- Increasing prevalence with increasing industrialization in developing countries

Source: Eichenfield LF, et al. *Pediatrics*. 2003;111:608-616.

mal Langerhans' cells, and dysregulation of phosphodiesterase. Two of these processes—excessive T-cell activation and hyperstimulation of T cells by atopic Langerhans' cells—are of particular interest in this discussion because blocking this reaction is the mechanism by which the new topical calcineurin inhibitors tacrolimus and pimecrolimus work.

In atopic dermatitis, the two subtypes of T cells primarily affected are T-helper type 2 (T_H2) cells, which are associated with the acute phase of disease, and T-helper type 1 (T_H1) cells, associated with the chronic phase (typified by the itch-scratch cycle and thickening of the skin). The shift from a T_H2 to a T_H1 cytokine profile in atopic dermatitis is quite fascinating, as these cytokines play a prominent role in the so-called hygiene hypothesis.

Atopic Dermatitis and the Hygiene Hypothesis

Developed from epidemiologic data, the hygiene hypothesis proposes that exposure to bacterial and viral infection early in life (e.g., via overcrowding and unhygienic contact) strengthens the immune system and thus may offer protection from atopic diseases. In recent years, its interpretation has been refined somewhat to embrace the idea that infections early in life promote development of T_H1 cytokines, whereas fewer infections early in life favor the development of T_H2 cytokines and atopy.

A recent review of epidemiologic data by Bach³ and an accompanying editorial by Weiss⁴ in *The New England Journal of Medicine* explored the association between a marked decrease in infectious diseases and a marked increase in the prevalence of autoimmune and allergic diseases since the 1950s. Of interest among Bach's findings were that measles may ameliorate the severity of nephrotic syndrome and atopic dermatitis, and that children who received antibiotics in infancy have a higher incidence of allergy and other atopic disorders than children who did not. He also

reviewed the literature on administration of probiotics as a means of decreasing the incidence of atopic dermatitis.

Some of the epidemiologic parallels between asthma and atopic dermatitis have been summarized in a recent review by this author and colleagues.⁵ These parallels include an increase in prevalence over the past 30 years in industrialized Western countries, higher prevalence in immigrants to Western countries than in their native lands, higher prevalence in urban than in rural areas, higher prevalence in privileged socioeconomic groups and smaller families,

“More than three quarters of children with atopic dermatitis may go on to develop asthma or allergic rhinitis.”

and increased prevalence with increased industrialization in developing countries (Table 1). This increase is more obvious in children and in young adults. Beyond the epidemiologic parallels, atopic dermatitis and asthma share immunopathophysiologic similarities such as IgE reactivity and T_H1/T_H2 cytokine response, as well as a genetic contribution (Table 2).

In summary, atopic dermatitis is clearly related to asthma. Atopic dermatitis is frequently the first manifestation of an atopic diathesis, which includes asthma and allergic rhinitis.⁵ More than three quarters of children with atopic dermatitis may go on to develop asthma or allergic rhinitis. Atopic dermatitis presentation usually peaks in the first 2 years of life, whereas asthma and gastrointestinal food allergies usually do not manifest until later in childhood. The trend for some patients with one allergic condition to metamorphose into another has been called the atopic march.

Table 2. Similarities Between Asthma and Atopic Dermatitis

- Target organ abnormalities:
 - Immunologic
 - IgE
 - T_H1/T_H2 cytokines
 - Inflammatory
 - Physiologic
- Genetic contribution

IgE = immunoglobulin E; T_H = T-helper type cell.
Source: Eichenfield LF, et al. *Pediatrics*. 2003;111:608-616.

Role of Exogenous Allergies in Atopic Dermatitis

Although the area of external allergens and how they affect atopic dermatitis is fraught with controversy, it cannot be argued that children with atopic dermatitis have a higher incidence of allergies to food and airborne allergens.

As many as 80% of children with asthma or atopic dermatitis are sensitized to inhalants such as dust mites, pollens, dander, and molds. Pediatric dermatologists, in particular, need to be aware that approximately one third of children with moderate to severe atopic dermatitis will have food allergies (eggs, milk, peanuts, soy, and wheat are the primary culprits in infants and young children). Food allergies are more likely in younger and more severe cases of atopic dermatitis.

Interestingly, even though this population has a higher incidence of food and inhalant allergies, the food or airborne allergen may not trigger eczematous dermatitis or atopic dermatitis when the patient is rechallenged. Reaction to exposure may take the form of urticaria, contact urticaria, or gastrointestinal symptoms. There have been a handful of documented cases of kwashiorkor in the United States in patients whose parents have tried to control their child's atopic dermatitis through elimination diets for food allergies. Fortunately, the introduction of calcineurin inhibitors (also known as topical immunomodulators) in the past few

years has allowed patients to maintain a disease-free state for longer periods, and parents are less concerned about trying to eliminate allergic triggers.

New Directions in Pathogenesis Research

Antimicrobial peptides known as cathelicidins and defensins are known to accumulate in the skin of patients with inflammatory skin diseases such as psoriasis. A recent study by Ong et al⁶ found, however, that levels of these peptides, which are natural defense proteins, were significantly decreased in the skin of patients with atopic dermatitis ($P=0.006$ in acute lesions and $P=0.03$ in chronic lesions). Immunologic process of atopic dermatitis produces interleukin 4 and interferon 13, both of which appear to have an inhibitory effect on cathelicidins and defensins. Downregulation of these natural defense proteins is shown to be correlated with the inability to combat *Staphylococcus aureus*. The authors concluded that this deficiency in the expression of antimicrobial peptides may explain why patients with atopic dermatitis are susceptible to *S. aureus* skin infections. They suggested that their findings highlight the importance of considering the interaction between the innate and adaptive immune systems in inflammatory skin diseases.

Evolving Atopic Dermatitis Therapy May Parallel Asthma Action Plan

This new understanding of the pathogenesis of atopic dermatitis is leading to new therapies focusing on early intervention and control of the inflammatory aspects of the disease, similar to the direction already taken in asthma treatment. The previously mentioned study that examined parallels between asthma and atopic dermatitis looked at the applicability of the asthma treatment model, as

laid out in asthma care guidelines developed by the National Heart, Lung, and Blood Institute of the National Institutes of Health, for atopic dermatitis treatment.⁵ The study noted that these care guidelines, first introduced in 1991, created heightened awareness of asthma as a disease of chronic inflammation, led to a unified approach to therapy, and stimulated new areas of research. The authors suggested that atopic dermatitis care guidelines could have a similar effect.

“...[T]he introduction of calcineurin inhibitors (also known as topical immunomodulators) in the past few years has allowed patients to maintain a disease-free state for longer periods...”

The asthma care guidelines have a three-tiered asthma action plan: maintenance medications all the time, an intervention strategy if flares occur, and a more aggressive treatment regimen if the intervention does not control the flares.⁷ For atopic dermatitis, a similar action plan also might have three tiers. The first level would be a low-level maintenance plan for milder cases, involving hydration and avoidance of allergens and intermittent low-potency topical corticosteroids or topical calcineurin inhibitors, and antihistamines. If the atopic dermatitis is not controlled by step 1, the next level of care would be a long-term maintenance therapy of topical calcineurin inhibitors, with topical corticosteroids used to control flares. The third level would be more aggressive therapy, involving higher-

potency topical corticosteroids, oral antibiotics, and possibly other regimens such as oral corticosteroids, oral cyclosporine, and perhaps in the future, a medication now being tested in trials, oral pimecrolimus.

As with asthma, the emphasis in this proposed atopic dermatitis action plan is on controlling inflammation. One of the tantalizing questions current research raises is whether long-term control of the inflammation of atopic dermatitis and maintenance of a disease-free state will influence the development of other atopic conditions. This is an intriguing idea, given the high prevalence of atopic conditions in the United States.

References

1. Leung DYM. Atopic dermatitis: New insights and opportunities for therapeutic intervention. *J Allergy Clin Immunol.* 2000;105:860-876.
2. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh).* 1980;92:44-47.
3. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med.* 2002;347:911-920.
4. Weiss ST. Eat dirt: The hygiene hypothesis and allergic diseases. *N Engl J Med.* 2002;347:930-931.
5. Eichenfield LF, Hanifin JM, Beck LA, et al. Atopic dermatitis and asthma: Parallels in the evolution of treatment. *Pediatrics.* 2003;111:608-616.
6. Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med.* 2002;347:1151-1160.
7. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.* Bethesda, MD: National Institutes of Health; 1997. Publication no. 97-4051.

With a complex disease such as atopic dermatitis, combination therapy is almost always the most effective way to treat patients. Depending on the severity of the disease, a treatment regimen might include one or more of the following therapies: hydration plus emollients, topical corticosteroids, antibiotics, ultraviolet (UV) light therapy, antihistamines, leukotriene inhibitors, and systemic immunosuppressants (Table 1). Each of these approaches will be discussed separately.

Hydration Plus Emollients

A 20-minute, warm soaking bath, followed by application of an emollient to damp skin within 3 minutes of emergence from the water, has been shown to have numerous benefits beyond hydration of the stratum corneum. It debrides and removes irritants to the skin, it increases penetration of topical corticosteroids, it may itself be corticosteroid-sparing, and it can have a relaxing effect on patients.

Emollients are the mainstay of atopic dermatitis therapy. They relieve pruritus and may be all the therapy the mildest cases require. The most occlusive emollients are ointments, followed by creams, gels, aerosols, and lotions. Because most patients prefer the feel of lotions, the practitioner must wage an education campaign to get patients to use the most effective product that is tolerable.

Topical Corticosteroids

Topical corticosteroids have been the treatment of choice for atopic dermatitis for decades. Although

promising new treatments such as the corticosteroid-free topical immunomodulators (also called calcineurin inhibitors) have emerged in recent years, it appears that topical corticosteroids will continue to constitute an important part of the treatment of patients with severe atopic dermatitis. (Dr. Belsito discusses calcineurin inhibitors in more detail elsewhere in this supplement.)

“...[T]he topical immunomodulators offer an alternative treatment option for atopic dermatitis on regions of the body where corticosteroids are contraindicated.”

Corticosteroids are ranked into seven classes of potency. More than 40 topical corticosteroids commonly used for atopic dermatitis are listed in the 1997 disease management practice parameters drafted by a joint task force of asthma, allergy, and immunology organizations.¹ However, a short list of the most frequently used agents for adults, listed from least to most potent, are triamcinolone acetonide 0.1% cream or ointment, fluticasone propionate cream or ointment, mometasone furoate cream 0.1%, fluocinonide 0.05% ointment, and clobetasol propionate 0.05% cream or ointment. For children, less potent topical corticosteroids are preferred. The most commonly used are hydrocortisone 1.0% or 2.5% ointment or cream,

hydrocortisone valerate 0.2% ointment or cream, fluticasone propionate 0.05% cream, and mometasone furoate 0.1% ointment or cream.

The primary concerns with topical corticosteroid use are side effects that include skin atrophy, telangiectasia, and striae. If applied to the eyelid or periorbital area, there is a risk of cataracts and glaucoma. Consequently, many practitioners do not like to use corticosteroids on the face, especially in children. There is also the danger that parents may not follow the physician's instructions and will apply the corticosteroid too aggressively or to an occluded area. Fortunately, the topical immunomodulators offer an alternative treatment option for atopic dermatitis on regions of the body where corticosteroids are contraindicated. They have been shown to be safe and effective on the face and neck in pediatric populations.

Antibiotics

Patients with acute flares of atopic dermatitis often have evidence of secondary bacterial infections. These skin infections are most commonly caused by *Staphylococcus aureus*, but streptococcal organisms may be present as well. Antibiotic therapy that targets both organisms (e.g., penicillins, erythromycins) is usually the most effective. Dr. Eichenfield discusses implications of *S. aureus* and immune response in patients with atopic dermatitis in his presentation, but suffice it to say that without a reduction in their bacterial loads in the skin, it is difficult for these patients to get better using only topical corticosteroids. (Azithromycin is the antibiotic of choice for this physician because of its ability to be delivered in high concentrations to macrophages and neutrophils relative to other antibiotics and the fact that it may be transported within phagocytes to areas of inflammation.²)

Table 1. Treatment of Atopic Dermatitis

- | | |
|---------------------------------------|--------------------------|
| • Bathing plus emollients to wet skin | • Antihistamines |
| • Topical corticosteroids | • Leukotriene inhibitors |
| • Antibiotics | • Immunosuppressants |
| • Ultraviolet light therapy | |

UV Light Therapy

The beneficial effects of UV light on patients with atopic dermatitis have been documented for more than a half-century. Since the 1970s, various light spectra have been actively investigated as adjunctive therapy for patients who are not responding to traditional treatments.

For acute, severe atopic dermatitis, three modalities have been shown to be effective: oral psoralen in combination with ultraviolet A (PUVA), a treatment long used for psoriasis; high-dose UVA1 (340 to 400 nM) therapy, typically 130 J/cm² daily for 15 days; and, more recently, photophoresis, also called extracorporeal photochemotherapy, a procedure that allows extracorporeal exposure of peripheral blood mononuclear leukocytes to UVA radiation.^{3,4,5}

For chronic and/or moderate atopic dermatitis, a number of modalities have been investigated, including broadband UVB, combination UVA/UVB therapy, low-dose UVA1, and more recently, narrow-band UVB (311 nM). Use of narrow-band UVB therapy appears to be on the increase. There is preliminary evidence that it not only is effective but may offer long-term remission or improvement of atopic dermatitis in some patients.³

Antihistamines

Antihistamines were once routinely prescribed for the treatment of atopic dermatitis because they block the H₁ receptors on the skin, and this was thought to relieve pruritus. Investigators now believe that T cells, monocytes, and eosinophils are the major effectors of the inflammatory cascade, not mast cells, and these agents thus do little to control pruritus. However, first-generation antihistamines are still being prescribed by some practitioners because their soporific effect is thought to interrupt the itch-scratch cycle.

Klein and Clark⁶ conducted an evidence-based review of antihistamines to see if the medications in fact relieved pruritus in patients with

atopic dermatitis. Of the 16 trials reviewed by the pair, none was a large, randomized, double-blind, placebo-controlled clinical trial that is considered the gold standard by researchers. Most of the trials were flawed in either sample size or study design. The authors concluded that the efficacy of antihistamines on pruritus by inducing sleep is based largely on anecdotal evidence and that there is no evidence to support the use of second-generation, nonsedating antihistamines in atopic dermatitis.

Leukotriene Inhibitors

Because leukotriene inhibitors such as zafirlukast have been used successfully to treat asthma and other inflammatory disorders, and, as previously noted, eosinophils are thought to play a role in effecting atopic dermatitis, these agents are being investigated as possible therapy for atopic dermatitis. Leukotriene inhibitors bind to the leukotriene receptors C4, D4, and E4, which increase vascular permeability and constrict smooth muscle.⁷ Carucci et al⁸ found that four patients with long-term atopic dermatitis improved after taking oral zafirlukast 20 mg twice daily for 2 weeks.

Zileuton is another leukotriene antagonist that is being investigated. It shuts down not only the C4, D4, and E4 receptors but also inhibits formation of the B4 receptor, which mobilizes neutrophils and eosinophils. Woodmansee and Simon⁹ found that patients taking zileuton 600 mg four times daily showed significant improvement in their atopic dermatitis, as measured by several outcome parameters. One of the newer drugs in this class, montelukast, also was found to effect a modest improvement in patients.¹⁰

Systemic Immunosuppressants

As is the case with conditions other than atopic dermatitis, the more severe the disease, the more aggressive the therapy. Systemic immunosuppressants have their place in the treatment armamentarium, but they can pose serious side effects.

A short course (7 to 10 days) of a systemic corticosteroid such as oral prednisone has been used for a long time to rein in severe atopic dermatitis while other therapies are being introduced. Patients usually respond quickly and dramatically, but overuse of systemic corticosteroids increases the risk of osteopenia,

Table 2. Use of Systemic Immunosuppressants in Atopic Dermatitis

- *Cyclosporine (CsA)*: Very effective and toxic; start at 5 mg/kg/d and reduce to 3 mg/kg/d or lower
- *Tacrolimus (FK506) (Tac)*: Effective and toxic; start at 0.1 mg/kg/d and reduce to 0.05 mg/kg/d or lower

SIDE EFFECTS: Tacrolimus vs. Cyclosporine

Nephrotoxicity:	Tac > CsA
Hypertension:	Tac ≥ CsA
Hyperglycemia:	Tac > CsA
Tremor, paresthesias, headache, insomnia:	Tac > CsA
Nausea, vomiting, diarrhea:	Tac > CsA
Hypomagnesemia:	Tac = CsA
Angina:	Tac > CsA
Arrhythmias:	CsA > Tac
Hyperlipidemia:	CsA > Tac
Hemolytic-Uremic Syndrome:	CsA
Hirsutism:	CsA
Alopecia:	Tac
Gingival hyperplasia:	CsA

cataracts, and other complications. The downside of systemic corticosteroids is that they work so well and so quickly that patients often do not want to switch over to the time-consuming, complicated, hydration/emollient/topical agent therapeutic regimen that is necessary for long-term management of atopic dermatitis. Further, if oral corticosteroids are reduced or eliminated without a corresponding increase in other therapies, there can be a strong rebound effect.

Two immunosuppressive drugs that researchers once predicted might be helpful in treating atopic dermatitis have thus far not lived up to expectations: methotrexate, a drug used to treat asthma and psoriasis, and azathioprine, used for rheumatoid arthritis.¹¹ A third immunosuppressive agent, mycophenolate mofetil, has been the subject of more recent investigations.^{12,13} In one open-label pilot study, 10 patients with moderate to severe atopic dermatitis that had not responded to traditional therapy took mycophenolate mofetil 1 g twice daily for 4 weeks; the dosage was then reduced to 500 mg twice daily for an additional 4 weeks.¹³ The regimen was shown to be highly effective in the seven patients who completed the study; their Scoring Atopic Dermatitis index was reduced by 74%. The agent has a slow onset of action, however, which patients may find frustrating.

Other immunosuppressants include the class of drugs known as macrolactam immunomodulators, which include cyclosporine, tacrolimus, and pimecrolimus. Elsewhere in this supplement, Dr. Belsito discusses the mechanism of action of these drugs and the use of the latter two in topical form. However, it will be noted briefly here that oral cyclosporine and oral tacrolimus have been used to treat very severe, refractory atopic dermatitis and other inflammatory dermatoses. Both of these agents have been shown to be effective but also highly toxic.^{1,14} The most serious

side effects are nephrotoxicity and hypertension, but other side effects may include hyperglycemia, tremors, paresthesia, insomnia, vomiting, diarrhea, hypomagnesemia, angina, arrhythmia, and hyperlipidemia (Table 2). Cyclosporine is usually started at 5 mg/kg daily, then reduced to 3 mg/kg when improvement is seen; tacrolimus is usually started at 0.1 mg/kg daily,

**“Better understanding
of the mechanisms
of atopic dermatitis
has led to new
treatment approaches...”**

then the dosage is reduced by half or more. Oral pimecrolimus, the subject of Dr. Gottlieb’s discussion elsewhere in this supplement, is also being examined for treatment of psoriasis.

Conclusion

Better understanding of the mechanisms of atopic dermatitis has led to new treatment approaches, although combination therapy is still the rule for most patients because of the complexity of the disease. Fortunately, most patients have mild to moderate disease and do not require some of the more aggressive, side effect-laden therapies outlined here.

References

1. Leung DY, Hanifin JM, Charlesworth EN, et al. Disease management of atopic dermatitis: A practice parameter. Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma, and Immunology. Work Group on Atopic Dermatitis. *Ann Allergy Asthma Immunol.* 1997;79:197-211.
2. Darmstadt GL. Antibiotics in the

- management of pediatric skin disease. *Dermatol Clin.* 1998;16:509-525.
3. Baron ED, Stevens SR. Light treatment modalities for atopic dermatitis. *Immunol Allergy Clin North Am.* 2002;22:1-15.
4. Krutmann J, Schopf E. High-dose UVA1 phototherapy: A novel and highly effective approach for the treatment of acute exacerbation of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh).* 1992;176:120-122.
5. Richter HI, Billmann-Eberwein C, Grewe M, et al. Successful monotherapy of severe and intractable atopic dermatitis by photopheresis. *J Am Acad Dermatol.* 1998;38:585-588.
6. Klein PA, Clark RA. An evidence-based review of the efficacy of antihistamines in relieving pruritus in atopic dermatitis. *Arch Dermatol.* 1999;135:1522-1525.
7. Henderson WR Jr. The role of leukotrienes in inflammation. *Ann Intern Med.* 1994;121:684-697.
8. Carucci JA, Washenik K, Weinstein A, Shupack J, Cohen DE. The leukotriene antagonist zafirlukast as a therapeutic agent for atopic dermatitis. *Arch Dermatol.* 1998;134:785-786.
9. Woodmansee DP, Simon RA. A pilot study examining the role of zileuton in atopic dermatitis. *Ann Allergy Asthma Immunol.* 1999;83:548-552.
10. Yanase DJ, David-Bajar K. The leukotriene antagonist montelukast as a therapeutic agent for atopic dermatitis. *J Am Acad Dermatol.* 2001;44:89-93.
11. Sidbury R, Hanifin JM. Old, new, and emerging therapies for atopic dermatitis. *Dermatol Clin.* 2000;18:1-11.
12. Grundmann-Kollmann M, Korting HC, Behrens S, et al. Successful treatment of severe refractory atopic dermatitis with mycophenolate mofetil. *Br J Dermatol.* 1999;141:175-176.
13. Grundmann-Kollmann M, Podda M, Ochsendorf F, Boehncke WH, Kaufmann R, Zollner TM. Mycophenolate mofetil is effective in the treatment of atopic dermatitis. *Arch Dermatol.* 2001;137:870-873.
14. Flores F, Kerdel FA. Other novel immunosuppressants. *Dermatol Clin.* 2000;18:475-483.

Corticosteroid-Free Topical Therapy in the Management of Atopic Dermatitis

Donald V. Belsito, MD

The family of macrolide immunosuppressants known as macrolactams includes cyclosporine, tacrolimus (formerly known as FK506), and pimecrolimus. The first two agents have a long history in oral form as medications to prevent allograft rejection after organ transplantation. Oral cyclosporine was first used to treat atopic dermatitis in 1987, but topical formulations have not proved successful in treating the disease.¹ Topical tacrolimus, however, has been far more effective and is without the increased risk of serious side effects that oral tacrolimus and cyclosporine pose. (Dr. Tharp discusses these side effects, which include nephrotoxicity and hypertension, elsewhere in this supplement.) Topical tacrolimus was approved by the U.S. Food and Drug Administration (FDA) for use in atopic dermatitis in late 2000.

The third agent, pimecrolimus, was the first of this family of immunomodulators to be developed specifically to treat inflammatory skin

diseases. It is sometimes recognized by its earlier name, the ascomycin SDZ ASM 981. It was chosen from hundreds of similar compounds for its highly skin-selective properties. The FDA approved topical pimecrolimus for atopic dermatitis treatment in 2001.

Penetration, Permeation of Pimecrolimus vs. Tacrolimus

When oral pimecrolimus is compared with oral tacrolimus in models of skin inflammation, it is twice as effective in the allergic contact dermatitis rat model and equally as effective in the allergic contact dermatitis mouse model. Yet when the two are compared in systemic immunosuppression models (graft vs. host, subcutaneous administration, or kidney transplant models, oral administration), pimecrolimus was found to have virtually no systemic effect, in contrast to tacrolimus.² In other words, even when pimecrolimus is administered systemically, it still works predominantly in skin tissue.

The selectivity of pimecrolimus for skin tissue over other organs, compared with that of tacrolimus, is believed to be because it is more lipophilic than the latter compound. In an in vitro study using pig skin, both drugs had approximately equal penetration into the epidermis, but pimecrolimus showed substantially less permeation through the epidermis and dermis than did tacrolimus.³

Mechanisms of Action of Calcineurin Inhibitors

The macrolactams pimecrolimus and tacrolimus are both calcineurin inhibitors. Once they are in the skin, they bind with a specific macrolipin, which then binds to the enzyme calcineurin. In atopic dermatitis, the inflammatory response is believed to begin when an antigen-presenting cell (atopic Langerhans' cell) hyperstimu-

lates a T-helper type 2 (T_H2) cell, upregulating cytosolic calcium (Table). This in turn activates the enzyme calcineurin that dephosphorylates the cytoplasmic nuclear factor of activated T cells (cNF-AT), which causes upregulated transcription of messenger ribonucleic acid (mRNA) for several proinflammatory cytokines. When pimecrolimus or tacrolimus bind up calcineurin, the enzyme cannot become activated and dephosphorylate cNF-AT, no matter how much the T cells are stimulated. As a result, proinflammatory cytokines are not produced and secreted.

Topical corticosteroids also affect the production and secretion of proinflammatory cytokines by deleterious effects on the Langerhans' and T cells. Unlike the calcineurin inhibitors, steroids interfere with collagen synthesis, which causes atrophy, and induce proliferation of endothelial cells, leading to telangiectasia. The thinner skin and dilated blood vessels that can occur with topical use of corticosteroids can result in systemic side effects. An apt metaphor for topical corticosteroids might be that they "cluster bomb" the immune response, rather than the selective "target bombing" that the calcineurin inhibitors provide.

Safety and Efficacy of the Calcineurin Inhibitors

As Dr. Tharp makes clear in his discussion of traditional therapies for the complex disease process that is atopic dermatitis, new approaches are being sought because there are so many limitations with existing combination therapies. According to a recent survey by the National Eczema Association for Science and Education (NEASE)⁴ of 4,000 of its members, 36% of patients considered over-the-counter therapies "not at all effective" and a third considered prescription therapy

Table. Rationale for Use of Macrolactams in Atopic Dermatitis

- Evolving understanding of pathogenesis of AD
 - Atopic Langerhans' cells hyperstimulate T_H2 cells
 - Excessive T_H2-cell activation by antigens →
 - ↑ IL-4 ↑ IL-5 & ↑ IL-3
 - ↑ serum IgE
 - eosinophilia
 - ↑ basophil spontaneous histamine release
 - chronic macrophage activation
 - ↓ number of IFN-γ-secreting T_H1 cells
 - ↓ cellular (T_H1)-mediated immunity

AD = atopic dermatitis; IFN-γ = interferon gamma; IgE = immunoglobulin E; IL = interleukin; T_H = T-helper type cell

“not at all effective” for their condition. A NEASE survey⁵ of more than 300 physicians known to prescribe topical corticosteroids found that 94% took special precautions when treating pediatric patients, 98% expressed major concern over long-term corticosteroid use, 91% were concerned about skin atrophy, and 80% were concerned with striae development.

In addition to these side effects, other side effects associated with long-term corticosteroid use include hypothalamic-pituitary-adrenal (HPA)-axis suppression (especially in children, because children have a higher body surface area-to-weight ratio than adults and because occlusion in diaper areas increases absorption) and resulting Cushing syndrome/growth retardation (Figure 1). A few years ago, a study testing a mid-potency corticosteroid on children was stopped before completion because of evidence of HPA-axis suppression within 3 weeks of twice-daily application of the medication. When used about the eye, there is a theoretical concern that topical corticosteroids may increase the risk of cataract and glaucoma. Finally, tachyphylaxis is also an issue with corticosteroids.

The topical calcineurin inhibitors, in contrast, appear to be safe and effective in both adult and pediatric populations, without the side effects associated with corticosteroids.¹ Human dermal safety studies for pimecrolimus, for example, have shown no evidence of cumulative irritancy, sensitization, phototoxicity, photoallergy, or skin atrophy.^{6,7}

Short-Term Pediatric and Infant Studies Using a Corticosteroid-Free Topical Immunomodulator

Topical pimecrolimus, in a 1% cream formulation, has been tested in two short-term, randomized, double-blind, vehicle-controlled, multicenter studies, one in 403 children 2 to 17 years of age and the other in 186 infants 3 to 23 months of age.^{8,9} In both studies, patients experienced significant pruritus relief, compared with vehicle by day 8 ($P \leq 0.001$ for

children and $P \leq 0.005$ for infants). It should be noted that patients may have experienced relief well before day 8 but that day 8 was the first day of evaluation for both studies.

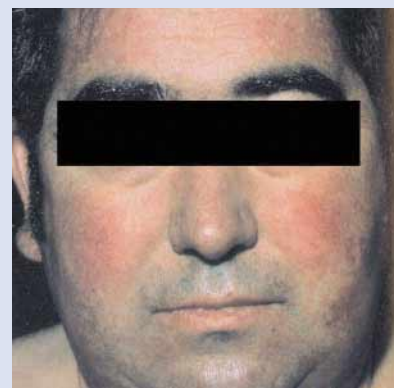
Several efficacy end points were used in the studies, but one parameter was the Eczema Area and Severity Index (EASI) score, which allowed for assessment of head and neck dermatitis severity relative to total body involvement. Pimecrolimus was shown to be particularly effective in clearing atopic dermatitis of the head and neck, especially in infants. The reason infants appear to respond better than older children is twofold: Infants' skin is more absorptive, and infants tend to have a more acute form of atopic dermatitis, with eczematous lesions that allow the medication to penetrate. In very thick, hyperkeratotic skin, topical macrolactams, including pimecrolimus, do not penetrate as effectively as do smaller molecules, such as corticosteroids.

In both studies, after the 6-week, double-blind phase, patients who had been on vehicle were allowed to switch to pimecrolimus in a 20-week, open-label phase. Once the patients who were on vehicle began using the active agent, they quickly achieved the results seen by those patients who had been on pimecrolimus from the beginning. Efficacy was maintained throughout the 20 weeks in both studies, demonstrating that tachyphylaxis is not an issue with pimecrolimus.

Long-Term Studies of Topical Immunomodulators

Several long-term, double-blind, controlled studies have examined whether pimecrolimus 1% cream could prevent or reduce atopic dermatitis flares. Two 12-month pediatric studies—one in 251 infants 3 to 23 months of age and the other in 713 children 2 to 17 years of age—and one 6-month study of 192 adults had similar study designs.^{10,11,12} Patients were divided into two groups. Both groups used emollients

Figure 1. Cushing Syndrome

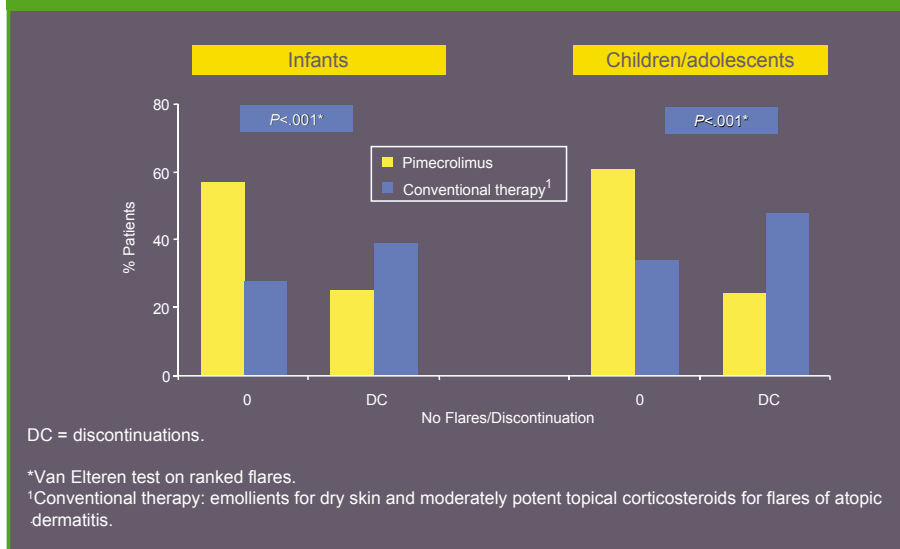


When used long term and applied over a large body surface area, topical corticosteroids may cause Cushing syndrome, among other side effects.

for dry skin. At the first onset of signs or symptoms of atopic dermatitis, patients used either pimecrolimus, if they were in the active medication group, or vehicle, if they were in the control group. In the event of flares beyond a specified level, both groups were permitted to use mid-potency corticosteroids. Efficacy end points included number of flares at 6 and 12 months (6 months only, for adult group), number of flares by disease severity at baseline, reduction in corticosteroid use, and improvement in EASI score. Safety assessments included recording adverse events and performing physical examinations and laboratory evaluations (clinical chemistry, hematology, and urinalysis) and, for the children's study only, performing a skin recall-antigen test at the conclusion of the study.

In all three studies, the patients using pimecrolimus experienced significantly fewer flares than did the control group ($P < 0.001$ for infants and children at 12 months, $P < 0.001$ for adults at 6 months). In fact, 57% of infants and 51% of children in the pimecrolimus group experienced no flares for a full year. Substantially more patients in the two pediatric control groups discontinued the study than did patients using pimecrolimus, despite the fact that they could use corticosteroids in the event of flares (Figure 2 on page 12).

Figure 2. Significantly Fewer Flares and Discontinuations with Pimecrolimus Over 12 Months



Results also were stratified by disease severity. Patients using pimecrolimus had significantly fewer flares than did those in the control group, regardless of whether their atopic dermatitis was ranked mild, moderate, or severe by the Investigator's Global Assessment. In the children's study, $P=0.002$ for mild and severe and $P\leq 0.001$ for moderate (P values for the infants' study are comparable). For adults, whose atopic dermatitis was rated moderate or severe, $P\leq 0.003$ for moderate and $P<0.013$ for severe.

In all three studies, overall corticosteroid use was substantially lower in the pimecrolimus group. In the infants' study, for example, 64% of the pimecrolimus group (vs. 35% of patients using vehicle) used no corticosteroids at all during the study period.

The safety data from these studies were equally encouraging. The most common application-site adverse event was burning, which in the children's study was reported in 10.5% of patients using pimecrolimus and 9.3% of those using vehicle. In the infants' study, more patients on vehicle complained of application-site burning (12.5%, vs. 10.4% for pimecrolimus). Given that patients with atopic dermatitis have hyperirritable skin and frequently report that even water or

petroleum jelly causes a stinging sensation, these percentages are not surprising. There were no significant increases in bacterial or viral skin infections with pimecrolimus. No systemic accumulations were seen over 12 months. In the children's study, in which a skin recall-antigen test was performed at study's end, there were no significant differences between the two treatment groups in response to recall antigens.

Conclusion

In summary, these clinical trials have demonstrated that pimecrolimus is effective and safe, as measured by numerous end points. It has rapid onset of action, particularly in the head and neck regions, with no evidence of the tachyphylaxis often experienced with corticosteroids. This suggests that a new paradigm may be appropriate for atopic dermatitis treatment, in which corticosteroid-free topical immunomodulators such as pimecrolimus and tacrolimus should be considered as first-line therapy, with corticosteroids used in the event of flares.

References

1. Sidbury R, Hanifin JM. Old, new, and emerging therapies for atopic dermatitis. *Dermatol Clin*. 2000;18:1-11.
2. Meingassner JG, Grassberger M,

Fahrngruber H, Moore HD, Schuuman H, Stuetz A. A novel anti-inflammatory drug, SDZ ASM 981, for the topical and oral treatment of skin diseases: in vivo pharmacology. *Br J Dermatol*. 1997;137:568-576.

3. Stuetz A. Pimecrolimus (Elidel, SDZ ASM 981): Preclinical pharmacologic profile and skin selectivity. *Semin Cutan Med Surg*. 2001;20:233-241.
4. 1999 Eczema Patient Survey. National Eczema Association for Science and Education. <http://www.nationaleczema.org/advocate/adv3q99.html>. Accessed March 20, 2003.
5. McAlister RO, Tofte SJ, Doyle JJ, Jackson A, Hanifin JM. Patient and physician perspectives vary on atopic dermatitis. *Cutis*. 2002;69(6):461-466.
6. Data on file, Novartis Pharmaceuticals Corp., East Hanover, NJ.
7. Queille-Roussel C, Paul C, Duteil L, et al. The new topical ascomycin derivative SDZ ASM 981 does not induce skin atrophy when applied to normal skin for 4 weeks: A randomized double-blind controlled study. *Br J Dermatol*. 2001;144:507-513.
8. Eichenfield LF, Lucky AW, Boguniewicz M, et al. Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. *J Am Acad Dermatol*. 2002;46:495-504.
9. Ho VC, Gupta A, Kaufmann R, et al. Safety and efficacy of nonsteroid pimecrolimus cream 1% in the treatment of atopic dermatitis in infants. *J Pediatr*. 2003;142:155-162.
10. Kapp A, Papp K, Bingham A, et al. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. *J Allergy Clin Immunol*. 2002;110:277-284.
11. Wahn U, Bos JD, Goodfield M, et al. Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. *Pediatrics*. 2002;110(1 pt 1):e2.
12. Meurer M, Fölster-Holst R, Bräutigam M. Pimecrolimus (ASM 981) cream improves disease control and quality of life in the long-term management of atopic dermatitis in adults. Poster presented at: 20th World Congress of Dermatology; July 1-5, 2002; Paris, France.

Potential Oral Treatment for Psoriasis and Atopic Dermatitis

Alice B. Gottlieb, MD, PhD

Oral cyclosporine has been studied for its efficacy in treating psoriasis since the mid-1980s. It is recommended for severe, recalcitrant plaque psoriasis, and it usually does an excellent job of clearing the skin, but the adverse effects associated with it are numerous and include renal dysfunction, hypertension, hirsutism, tremor, gingival hyperplasia, musculoskeletal pain, paresthesia, microangiopathic hemolytic anemia, hyperlipidemia, hypomagnesemia, thrombocytopenia, headache, leg cramps, dizziness, abdominal pain, and diarrhea.¹ Long-term use of cyclosporine has demonstrated evidence of nephropathy in 21% of patients, and increased blood creatinine levels, reflecting a reduction in glomerular filtration rate, have been reported in 18% of patients.¹ Oral tacrolimus also has been used successfully in psoriasis treatment, but side effects resemble those seen for cyclosporine.²

Because of these concerns, alternative treatments that work as effectively as cyclosporine but with fewer side effects are being actively investigated.

Pimecrolimus is a member of the immunosuppressive macrolide family that includes cyclosporine and tacrolimus. Pimecrolimus is an

ascomycin derivative that selectively inhibits inflammatory cytokine release. Topical pimecrolimus cream has been approved for use in the United States for atopic dermatitis and has also been investigated in Europe for the treatment of psoriasis.^{3,4} However, oral administration of pimecrolimus in humans had not been evaluated until Rappersberger et al⁵ conducted a phase I/II randomized, double-blind, placebo-controlled, multiple rising doses proof-of-concept study for treatment of psoriasis.

“...[A]lternative treatments that work as effectively as cyclosporine but with fewer side effects are being actively investigated.”

Novel Oral Antiinflammatory Tested for Safety and Efficacy in Humans

The purpose of the Rappersberger study was to find out if pimecrolimus, which had demonstrated high anti-inflammatory activity but low potential for immunosuppression when

administered systemically in animal models, would be safe and effective in psoriasis and possibly other inflammatory skin diseases as well.⁵ In the 6-week study, five consecutive cohorts of 10 patients were treated with rising doses of oral pimecrolimus or placebo for 4 weeks. (In each cohort, eight patients received active medication and two received placebo.) Escalating doses were 5 mg, 10 mg, or 20 mg once daily, and 20 mg or 30 mg twice daily. The next-higher dose level was started only after the preceding dose was shown to be safe and tolerable. Patients were hospitalized for the first 2 weeks of the study and followed for 2 weeks after treatment ended.

Efficacy was measured by Psoriasis Area and Severity Index (PASI). Numerous safety parameters were used to evaluate safety and tolerability, including physical examination, blood pressure, electrocardiogram (ECG), blood biochemistry, hematology, urinalysis, glomerular filtration rate, renal plasma flow, and glucose tolerance tests.

To participate in the study, patients had to have moderate to severe chronic, stable, plaque-type psoriasis and could not have other concurrent diseases such as hypertension, diabetes, or hyperlipidemia. It should be noted that these patients were fairly healthy and thus may not be representative of the general population.

The data showed there was clear clinical efficacy in patients receiving the highest doses of pimecrolimus, with a reduction in PASI scores of 60% for those on the 20-mg twice-daily regimen and of 75% for patients on 30 mg twice daily. Three patients achieved complete clearance. There were no clinically significant changes in physical examination, blood pressure, ECG, or the laboratory tests related to renal function, such as serum creatinine, glomerular filtration rate, or renal

Figure 1. Oral Immunomodulator to Treat Psoriasis



This patient experienced 60% reduction in Psoriasis Area and Severity Index score after 4 weeks' treatment with 40 mg oral pimecrolimus. Photo on left is at baseline; photo, right, shows day 28.

Source: Rappersberger K, et al. Pimecrolimus identifies a common genomic anti-inflammatory profile, is clinically highly effective in psoriasis and is well tolerated. *J Invest Dermatol.* 2002;119:876-887. Used with permission.

Figure 2. Psoriasis of the Knee



This patient experienced 75% reduction in Psoriasis Area and Severity Index score after 4 weeks' treatment with 60 mg oral pimecrolimus. Top photo is at baseline; bottom photo shows day 28.

Source: Rappersberger K, et al. Pimecrolimus identifies a common genomic anti-inflammatory profile, is clinically highly effective in psoriasis and is well tolerated. *J Invest Dermatol.* 2002;119:876-887. Used with permission.

plasma flow. There was no effect on glucose tolerance and no serious adverse events. The one notable side effect was a transient feeling of warmth by patients after taking the drug. Pharmacokinetic assessments found that pimecrolimus was rapidly absorbed; a steady state of pimecrolimus was reached after 5 to 10 days, C_{MAX} , and area under the curve from 0 to 24 hours was 54.5 ng/mL, at steady state and 589.9 ng/mL, respectively, at steady state at the highest dose. There was no psoriasis rebound observed.

Novel Oral Antiinflammatory Subject of 12-Week Psoriasis Study

Based on these encouraging results, two international, multicenter dose-finding studies were launched, one testing oral pimecrolimus for psoriasis and one for atopic dermatitis.⁶

The psoriasis study was a randomized, double-blind, placebo-con-

trolled, parallel-group dose-finding study in 142 otherwise healthy patients (in particular, without any hypertension, hyperlipidemia, or diabetes) with moderate to severe psoriasis. The study consisted of four arms: placebo, 10 mg, 20 mg, and 30 mg pimecrolimus twice daily. A 12-week double-blind phase was followed by a 12-week posttreatment follow-up phase. The primary efficacy end point was week 7. Efficacy was assessed via PASI score, Investigator's Global Assessment (IGA), and subject assessment. Safety was evaluated with laboratory tests and other tests similar to those in the Rappersberger study but also included a skin allergy test.

An evaluation of participant discontinuations showed that twice as many patients taking the placebo dropped out as did patients on active medication. Unsatisfactory therapeutic effect was the reason most commonly cited.

In looking at efficacy end points, a summary of PASI results showed:

- Reductions in both mean and median percentage change from baseline, indicating a clear dose-response relationship (Figure 3).
- The primary end point, week 7 mean reduction in PASI scores, was highly significant for both 20-mg and 30-mg twice-daily groups ($P < 0.001$).
- Marked clinical effect by week 5, with a plateau by week 9.

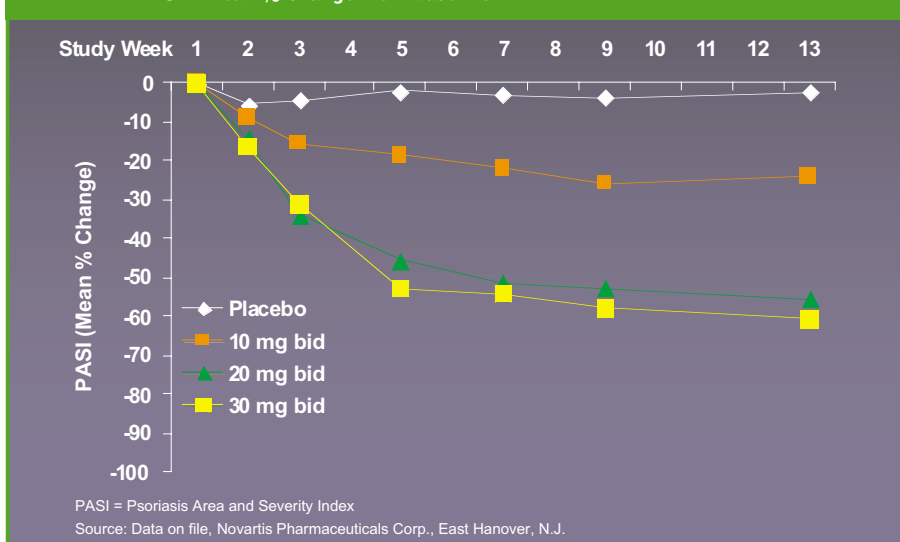
- Impressive and clinically significant maximal reduction in PASI scores with the two highest dose groups (up to 80% median reduction in 30-mg twice-daily group).

The percentage change in PASI scores seen in this study rivals the results that oral cyclosporine has demonstrated historically.

The percentage of patients rated clear or almost clear by IGA also showed a dose-response relationship. At week 7, no patients on placebo or 10 mg twice daily were clear, compared with 4 of the patients receiving 20 mg twice daily and 10 patients receiving 30 mg twice daily. At week 13, the number of patients rated clear or almost clear totaled 3, 8, and 15, respectively, for the 10-mg, 20-mg, and 30-mg twice-daily dosages. No patients on placebo were rated clear by week 13. It should be noted that IGA of clear or almost clear is a very strict criterion for success for patients experiencing this highly inflammatory type of psoriasis.

As noted earlier, subject assessment was another efficacy indicator. A significant treatment effect and dose response was discerned by patients as early as the first return visit, which occurred the second week of the study. Treatment differences for the 20-mg and 30-mg twice-daily groups were even more pronounced by this assessment than by IGA.

Figure 3. Oral Pimecrolimus Study for Psoriasis
PASI - mean % change from baseline



Safety Analysis of Pooled Results

The safety results of the 12-week treatment phases of both the psoriasis and the atopic dermatitis trials were pooled for analysis, thus covering the outcomes of a total of 243 patients.⁶ Only two serious adverse events were reported, both of which occurred in the placebo group. Among side effects reported, headache was the most common complaint in all four patient groups (including placebo), but it did not show a clear dose relationship. Patients receiving the higher doses of pimecrolimus reported the transient feeling of warmth that Rappersberger and colleagues had noted in their study. Nausea and gastrointestinal upset also were reported in the active medication group and appeared to show a dose-response effect. Infections appeared to be increased in the 30-mg twice-daily group. Most of the infections occurred in patients with atopic dermatitis, not psoriasis, and most infections seemed to be in the form of folliculitis, furuncles, and related skin infections.

Particular attention was paid to blood glucose and renal function in the safety analysis, as the pancreas and kidneys were identified as target organs in preclinical studies. Investigators found that mean serum creatinine levels remained fairly consistent throughout the duration of both studies.

One patient in the placebo group and three patients in the 30-mg twice-daily group exhibited a $\geq 30\%$ increase in serum creatinine levels over the 12-week treatment period. This is in contrast to approximately 20% of patients taking oral cyclosporine who experienced a $\geq 30\%$ increase in serum creatinine levels in the same time frame.

(However, it should be noted that the cyclosporine studies included patients with hypertension and other comorbid illnesses.) There was no modification of oral blood glucose tolerance in any treatment group.

The hypertension evaluation showed that pimecrolimus appeared to have no effect on blood pressure. Skin allergy testing showed that immune response to bacterial and fungal antigens remained intact during pimecrolimus treatment.

In summary, the safety findings for the two trials showed that oral pimecrolimus has a good safety profile.

Conclusion

It is hoped that the promising results of these early trials will pave the way for larger phase III trials with patients more representative of the general population. Psoriasis has a considerable degree of comorbidity associated with it, and oral pimecrolimus should be tested in patients with controlled hypertension, hyperlipidemia, diabetes, and similar conditions if it is to be compared with oral cyclosporine. Long-term data are needed to test safety and efficacy after 1 year or more of treatment. Pediatric trials and psoriatic arthritis trials are also called for to see whether these special populations can benefit from this medication.

References

1. Lebwohl M, Ellis C, Gottlieb A, et al. Cyclosporin consensus conference: With emphasis on the treatment of psoriasis. *J Am Acad Dermatol*. 1998;39:464-465.
2. Lebwohl M, Ali S. Treatment of psoriasis. Part 2: Systemic therapies. *J Am Acad Dermatol*. 2001;45:649-651.
3. Rappersberger K, Meingassner JG, Fialla R, et al. Clearing of psoriasis by

Figure 4. Atopic Dermatitis of the Neck



Adult male at baseline, top, and one week after completion of a 12-week study of oral pimecrolimus for atopic dermatitis.

Photo courtesy Klaus Wolff, MD, FRCP, University of Vienna, Austria

a novel immunosuppressive macrolide. *J Invest Dermatol*. 1996;106:701-710.

4. Mrowietz U, Graeber M, Bräutigam M, et al. The novel ascomycin derivative SDZ ASM 981 is effective for psoriasis when used topically under occlusion. *Br J Dermatol*. 1998;139:992-996.
5. Rappersberger K, Komar M, Ebelin ME, et al. Pimecrolimus identifies a common genomic anti-inflammatory profile, is clinically highly effective in psoriasis and is well tolerated. *J Invest Dermatol*. 2002;119:876-887.
6. Data on file, Novartis Pharmaceuticals Corp., East Hanover, NJ.

New Strategies in the Management of Inflammatory Skin Diseases CME Post-Test and Evaluation

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INSTRUCTIONS: For each question or incomplete statement, one answer or completion is correct. Seven out of 10 correct responses are required for credit. Circle the most appropriate response.

- Early age of onset and atopy are two of the four characteristics described as "important features" for diagnosing atopic dermatitis using new criteria devised at an American Academy of Dermatology consensus conference. What are the other two important features?
 - Xerosis and keratosis pilaris
 - Tendency toward cutaneous infections and changes in facial pallor
 - Xerosis and serum IgE reactivity
 - Keratosis pilaris and cheilitis
- Which of the following epidemiologic parallels between atopic dermatitis and asthma were documented in a recent *Pediatrics* review by Eichenfield and colleagues?
 - Higher prevalence in immigrants to Western countries than in their native lands
 - Higher prevalence in rural areas
 - Higher prevalence in socioeconomically disadvantaged families
 - All of the above
- According to a review by Klein and Clark, how many randomized, double-blind, placebo-controlled clinical trials have examined the efficacy of oral antihistamines in treating atopic dermatitis?
 - 0
 - 4
 - 6
 - 13
- Which of the following agents are leukotriene inhibitors that have been studied for atopic dermatitis therapy?
 - Zafirlukast
 - Zileuton
 - Montelukast
 - All of the above
- Which of the following statements accurately describes a typical limitation of oral corticosteroids in treating atopic dermatitis?
 - Slow onset of action
 - Rebound flares when medication is withdrawn
 - Cannot be used in conjunction with topical macrolide therapies
 - Cause nausea and vomiting
- How does tacrolimus differ from pimecrolimus?
 - Tacrolimus is more lipophilic than pimecrolimus.
 - Animal models have shown tacrolimus to be less immunosuppressive than pimecrolimus when administered systemically.
 - Tacrolimus is a calcineurin inhibitor; pimecrolimus blocks H₁ receptors.
 - In pig skin studies, tacrolimus showed more permeation through the epidermis and dermis than pimecrolimus.
- Which of the following statements best describes findings of two short-term pediatric studies using topical pimecrolimus?
 - Pimecrolimus was shown to be especially effective in clearing head and neck atopic dermatitis.
 - Older children with more lichenified skin responded better to treatment than did children with acute lesions.
 - Both studies showed rapid clearing of skin, but efficacy could not be maintained after week 6, indicating tachyphylaxis may be an issue.
 - Although children treated with pimecrolimus experienced more pruritus relief than the control groups, the difference was deemed not statistically significant.
- In a 12-month trial that looked at whether topical pimecrolimus reduced or prevented flares in infants, what percentage of patients used no corticosteroids at all during the study?
 - 35%
 - 57%
 - 64%
 - 75%
- Which of the following side effects is not associated with oral cyclosporine use?
 - Gingival hyperplasia
 - Alopecia
 - Diarrhea
 - Paresthesia
- Which of the following statements does not reflect the findings of Rappersberger and colleagues' study of oral pimecrolimus for the treatment of psoriasis?
 - A transient feeling of warmth was noted by patients taking active medication.
 - Oral pimecrolimus had no effect on glucose tolerance.
 - PASI scores were reduced by 75% in patients taking the 30-mg dose twice daily.
 - Rebound psoriasis was observed 6 weeks after treatment ended.

PROGRAM EVALUATION

We would appreciate your answering the following questions in order to help us plan for other activities of this type.

- How would you rate the clarity of the presentation of the material? (Please check.)

	Excellent	Good	Fair	Poor
Text	_____	_____	_____	_____
Images	_____	_____	_____	_____
Post-Test	_____	_____	_____	_____

- How would you rate the clinical relevance of the material?

- How would you rate this material, compared with similar independent study presentations in print format?

- Was this a fair and balanced presentation? Please comment on the scientific rigor, fairness, and balance of the material.

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