

NEW TREATMENTS FOR ATOPIC DERMATITIS

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The pathogenesis of atopic dermatitis (AD) is a complex inflammatory process involving resident and infiltrating cells of the skin, including keratinocytes, Langerhans' cells; lymphocytes, mast cells, eosinophils; and cytokines, chemokines, and other mediators (see article by Leung elsewhere in this issue).²² As in other allergic diseases, the inflammatory infiltrate reflects a predominant Th2 cytokine profile, but unlike in other allergic diseases, Th1 cytokines also have a role. Therapies for AD must target this complex inflammatory process.

The mainstay of therapy for AD is skin hydration, avoidance of irritants, and use of topical steroids (see article by Boguniewicz and Nicol elsewhere in this issue). Topical steroids are not always effective and can lead to significant topical and systemic side effects. They may cause cutaneous atrophy, striae, bruisability, and telangiectasia of the skin. High-potency topical steroids can lead to systemic absorption and growth suppression in children. Alternative anti-inflammatory agents would be beneficial. This article discusses new topical immunomodulators and other novel therapies for AD, including the following:

Topical immunomodulators:

Topical tacrolimus (FK506, Protopic)

Topical pimecrolimus (ASM981, Elidel)

Systemic immunomodulators:

Mycophenolate mofetil (MMF; CellCEPT)

Interferon-gamma (IFN- γ)

Intravenous immunoglobulin (IVIg)

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Other therapies

- Leukotriene antagonists
- Probiotics

TOPICAL IMMUNOMODULATORS

Oral cyclosporine is an effective steroid-sparing agent for severe refractory AD; however, concerns about renal and hepatic toxicity limit its chronic usage.³ Early studies with topical cyclosporine were not effective, but other agents show great promise topically. Topical immunomodulators are a new class of agents that act locally on T cells by suppressing cytokine transcription. The two most studied topical immunomodulators are topical tacrolimus (Protopic, Fujisawa Healthcare, Inc, Deerfield, Illinois) and SDZ ASM 981 (pimecrolimus, Elidel Novartis Pharmaceuticals Corporation, East Hanover, New Jersey). Tacrolimus binds to the cytoplasmic protein FK506 binding protein, and the resulting complex inhibits calcineurin, which normally dephosphorylates NFAT, a major cytokine transcription factor. SDZ ASM 981 acts in a similar fashion and binds its immunophilin (macrophilin-12) to inhibit calcineurin and suppress cytokine production.

Topical Tacrolimus

Tacrolimus has been used to prevent organ rejection after liver and kidney transplants and to prevent graft-versus-host disease after bone marrow transplantation. Systemic administration of tacrolimus can result in side effects such as renal function impairment, hypertension, and abnormal glucose tolerance. Topical use in patients with AD does not seem to cause systemic effects. Tacrolimus also inhibits degranulation and the synthesis of mast cell mediators and cytokines.⁴² In vitro tacrolimus decreases the expression of activation molecules such as interleukin-2 receptor (IL-2R) (CD25), CD80, CD40, and MHC class I and II.³⁴ In contrast, betamethasone valerate is shown to increase the expression of CD25, MHC class II, and CD80. Tacrolimus is about 100 times more potent in vitro than betamethasone valerate at inhibiting the stimulatory function of Langerhans' cells.³⁴ In skin biopsies from patients who responded to topical tacrolimus, a decrease was found in the expression of the high-affinity receptor for IgE on Langerhans' cells and inflammatory dendritic epidermal cells (IDECs).⁴⁹

Another mechanism of action of tacrolimus may involve staphylococcal superantigens. Hauk and Leung have shown that, unlike dexamethasone, tacrolimus has an inhibitory effect on proliferation induced by staphylococcal enterotoxin B in peripheral blood mononuclear cells (PBMcs) from patients with AD and healthy volunteers.¹⁵ This finding may explain why patients who are resistant to topical corticosteroids respond to topical tacrolimus. Staphylococcal colonization also has been

shown to decrease in AD treated with topical tacrolimus.³⁷ Topical tacrolimus does not affect the fibroblasts and thus does not cause atrophy of the skin.³⁵ Neither systemic nor topical tacrolimus cause the hypertrichosis seen with systemic cyclosporine administration.

Several studies have demonstrated the safety and efficacy of topical tacrolimus in patients with AD. Topical tacrolimus has been studied in more than 10,000 patients worldwide. The improvement in AD has been rapid and is seen within the first week of treatment as a marked decrease in erythema. Two early short-term studies, one in adults and one in children, evaluated the use of three concentrations of topical tacrolimus (0.03%, 0.1%, 0.3%) in comparison with placebo. Boguniewicz et al found that the mean percent improvement for a modified Eczema Area and Severity Index (EASI) for each of the tacrolimus groups (0.03%, 72%; 0.1%, 77%; 0.3%, 81%) was significantly better than that of the vehicle group (26%; $P < 0.001$).⁴ Ruzicka et al reported similar results with a decrease in the summary score for trunk and extremity dermatitis for the tacrolimus groups (0.03%, 67%; 0.1%, 83%; 0.3%, 75%) that was significantly greater than that for the placebo group (22.5%; $P < 0.001$).³⁸ Tacrolimus blood concentrations were low for most patients throughout the study. A trend suggested there was more absorption at the higher concentration, and subsequent phase III studies were performed using topical tacrolimus concentrations of 0.03% and 0.1%, compared with placebo. These studies involved 632 adult patients aged 15 to 79 years and 351 patients aged 2 to 15 years who had moderate-to-severe AD.^{13, 32, 43} The patients applied topical tacrolimus twice daily to AD lesions and then 7 additional days after clearing. In the pediatric study, 61% of the patients had severe AD at baseline, and the mean percentage body surface area involvement was 47.7%.³² Greater than 90% improvement was seen in 36% (0.03%) to 41% (0.1%) of patients in tacrolimus groups in comparison with 8% of patients in the vehicle group ($P < 0.001$). A significantly greater percentage of patients in the tacrolimus groups (0.03%, 73%; 0.1%, 78%) had at least moderate improvement in comparison with the vehicle group (26.7%; $P < 0.001$). Significantly greater improvement in the tacrolimus groups also was found for all other efficacy parameters, including EASI score, total score, percentage of body surface area affected, and patient assessment of pruritus. Similar findings were observed in the adult studies.¹³ About 55% of patients had severe AD at baseline, and the mean percentage body surface area involved was 45%. A significantly greater number of patients in the tacrolimus groups showed at least moderate improvement in comparison with the vehicle group (0.03%, 62%; 0.1%, 73%; vehicle group, 20%). Unlike the pediatric study, there was evidence for a difference in efficacy between the two concentrations of tacrolimus. The difference in efficacy between the 0.1% and 0.03% ointment was noted in adults patients with severe disease at baseline, with extensive body surface area involvement at baseline and in black patients.¹³

Studies document that effectiveness is maintained for periods of up to 1 year. Kang et al treated 255 children aged 2 to 15 years with

moderate-to-severe AD with topical 0.1% tacrolimus ointment twice daily for up to 12 months.²¹ Significant improvement in signs and symptoms of AD, percentage of body surface area involved, and pruritus were found during the first week of treatment and were maintained throughout the study. Sixty-one patients had investigator-documented complete clearing of AD during the study, and treatment with tacrolimus ointment was discontinued. The median time to clearing was 92 days. Forty of these patients had an investigator-documented recurrence with a mean time to recurrence of 54.5 days. There was no indication of a rebound flair, and patients had a milder presentation of AD recurrence. Reitamo et al investigated the efficacy of 0.1% tacrolimus ointment for long-term monotherapy in adults with AD.³⁶ This study involved 316 patients aged 18 to 70 years. The EASI scores and percentage of affected body surface area continued to decrease until the third month, and this improvement was maintained during the rest of the study. Ointment use also decreased, with a median daily ointment use of 3.9 g during month 1 and 2.3 g during month 12. In a subset of patients in this trial, reduction in *Staphylococcus* colonization also was reported.

In the topical tacrolimus studies, there were no chronic skin changes and no significant systemic side effects.^{32, 36, 43} Topical tacrolimus does not effect fibroblasts, and atrophy, pigment changes, or telangiectasia have not been seen. No significant systemic absorption was found with short- or long-term use. No clinically meaningful changes in laboratory parameters were observed in the studies. Tacrolimus blood concentration levels were nondetectable or low, which is consistent with minimal absorption of tacrolimus through affected skin. Of approximately 400 samples in the pediatric studies, only two samples had levels greater than 2 ng/ml but less than 5 ng/ml, and 97% of samples had levels less than 1 ng/ml.^{4, 33, 2} In comparison, the therapeutic range of oral tacrolimus for transplantation is 5 to 15 ng/mL. The blood levels above 1 ng tended to occur early in the treatment and decreased with time. Similar findings were found in adult samples, with only 2% of 500 samples with levels above 2 ng/mL. Caution must be exercised for patients with defective skin barriers, such as patients with Netherton's syndrome in whom higher levels of tacrolimus have been reported.¹ Application-site events, including itching and burning, were noted in up to 57% of patients but typically lasted less than 15 minutes after application, resolved after a few days of therapy, and rarely resulted in study discontinuation.⁴³

Other statistically significant adverse events found in the pediatric studies included varicella, vesiculobullous rash, and sinusitis.³³ Varicella was seen in 6 of 1:18 patients in the 0.03% group in comparison with no patients in vehicle group and 1 patient in the 0.1% group. Because this statistically significant difference was seen only in the lower-dose group, it is likely that the cases occurred randomly and are not drug or dose related. All of these patients were under 8 years of age and had uncomplicated courses of varicella. Sinusitis was seen less commonly in the tacrolimus groups (1% in the 0.1% group; 3.3% in the 0.03% group; 8%

in the vehicle group). It is likely that this finding results from random events rather than drug- or dose-related effects. Vesiculobullous rash was noted in 3.8% of the 0.03% group and 1% of the 0.1% group in comparison with 0% in the vehicle group. This percentage included two patients in the 0.03% group who developed eczema herpeticum, which occurs in patients with AD.

In the adult studies, flu-like symptoms, headache, and skin tingling were reported more commonly in the 0.1% group than the 0.03% or vehicle groups.⁴³ Alcohol intolerance, hyperesthesia, and folliculitis were noted in the 0.03% and 0.1% groups. Transplant patients taking oral tacrolimus have an increased risk for developing lymphoma. In the clinical studies of topical tacrolimus, less than 1% of patients were reported to have lymphadenopathy, which generally was related to skin infections.

In mouse dermal carcinogenicity studies, median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing with high levels of tacrolimus and concurrent exposure to ultraviolet (UV) radiation (Protopic package insert, Fujisawa Healthcare, Deerfield, Illinois). In the mouse studies, topical application of tacrolimus was not associated with skin tumor formation under ambient room lighting (Protopic package insert, Fujisawa Healthcare). No phototoxicity or photoallergy have been detected in clinical trials.² Nonetheless, sun-screen use is recommended to minimize risk of skin cancers.

In December 2000, the Food and Drug Administration (FDA) approved tacrolimus ointment for short-term and intermittent long-term therapy in the treatment of patients aged 2 years and older with moderate-to-severe AD for whom "the use of alternative, conventional therapies is deemed inadvisable because of potential risks" and for those "who are not adequately responsive to or intolerant of alternative, conventional therapies."^{*} Patients likely to benefit from topical tacrolimus include patients with facial and intertriginous AD in whom there is greater concern about topical steroid-induced atrophy, patients unresponsive to topical steroids, and patients with severe AD who require chronic high-potency topical steroids.

Before or at the time of starting tacrolimus, patients may benefit from a course of oral antibiotics if an active skin infection is present. Topical tacrolimus should not be applied to skin sites with obvious viral infections (e.g., herpes, molluscum). Patients should be instructed in the appropriate use of tacrolimus ointment. The patient information sheet on Protopic is helpful and can be found at <http://www.protopic.com>. Patients should apply the ointment twice daily until lesions clear and then twice daily for an additional 7 days after clearing. To minimize local side effects, the skin should be dry before application. Applying in the direction of the hair follicles may be helpful for patients who develop folliculitis from the ointment. Patients should be warned about side effects, including alcohol intolerance (redness, flushing of the face when

^{*}The 0.03% strength is indicated for pediatric patients.

drinking alcohol; 4% of adults in the 0.1% group) and transient local side effects (transient burning and pruritus that diminishes with time). Pretreatment with antihistamines and analgesics may be useful. Patients should use sun protection such as clothing, hats, and sunscreen.

Topical Pimecrolimus

Another promising therapy is SDZ ASM981 (pimecrolimus, Elidel). Pimecrolimus inhibits T-cell and mast-cell activation by blocking synthesis and release of inflammatory cytokines.¹⁰ It seems to exhibit a high skin-specific anti-inflammatory activity with low potential for affecting the systemic immune response.²⁷ Like topical tacrolimus, it does not cause skin atrophy. Minimal systemic absorption has been observed. In contrast to cyclosporine and tacrolimus, pimecrolimus shows low potential for systemic immunosuppression in animal models.²⁷ Topical application in the animal models inhibits skin inflammation and is comparable to that of a potent topical steroid.²⁶

In an adult side-to-side comparison study, twice daily application of 1% pimecrolimus cream resulted in significant improvement compared with the vehicle group.⁴⁷ Further studies have shown the efficacy and safety of pimecrolimus in AD. A double-blind, randomized, parallel-group, multicenter dose-finding study was done in Europe. In this study, 260 patients were assigned randomly to treatment with topical pimecrolimus at concentrations of 0.05%, 0.2%, 0.6%, or 1.0%, vehicle cream, or betamethasone-17-valerate cream.²³ Patients were treated twice daily for 3 weeks. For the EASI, the 0.2%, 0.6%, and 1.0% pimecrolimus creams were more effective than the vehicle cream ($P = 0.041$, 0.001, and 0.008, respectively). The 1.0% cream was the most effective pimecrolimus concentration; however, the topical steroid cream was more effective than the pimecrolimus creams tested in this study. Burning or a feeling of warmth were the only adverse events reported more often in the 0.6% and 1.0% pimecrolimus groups than in the vehicle group (42.9%, 48.9%, and 34.9%, respectively). On the basis of this trial, the 1.0% concentration was chosen for the Phase III trials. A 6-week trial of approximately 400 children aged 18 months to 17 years found improvement in all efficacy parameters in the 1.0% pimecrolimus group in comparison with the vehicle group.⁶ Most children had mild or moderate AD at baseline. A significantly greater percentage of patients in the pimecrolimus group were rated as clear or almost clear (35% in pimecrolimus group and 18% in the vehicle group; $P < 0.05$). Mean reduction in the EASI score at 6 weeks was 45% in the pimecrolimus group versus 1% for vehicle group ($P < 0.001$). Pimecrolimus was well tolerated with minimal application-site adverse effects. There was no difference between vehicle and pimecrolimus creams in application-site events. Application-site burning was noted in 10.9% of patients in pimecrolimus group and 12.5% of patients in the vehicle group. Pharmacokinetic studies of pimecrolimus in patients as young as 3 months of age have been done. In one report, blood

concentrations of pimecrolimus over a 3-week period were found to be low in children with AD aged 1 to 4 years, even with extensive skin involvement.^{14a}

SYSTEMIC IMMUNOMODULATORS

Mycophenolate Mofetil

A pilot study documented the efficacy of MMF (Cell CEPT, Hoffman LaRoche, Germany).²⁹ MMF is an inhibitor of inosine monophosphate dehydrogenase. It interferes with de novo purine biosynthesis and inhibits the synthesis of guanosine monophosphate. Lymphocytes depend on de novo purine biosynthesis and are affected significantly by the action of MMF. Ten patients with severe AD were evaluated in the pilot study. They received an initial dose of 1 g of oral MMF daily during the first week and 2 g daily for another 11 weeks. Compared with baseline, the median scores for disease severity (SCORAD index) improved by 68% during treatment with MMF. MMF also produced a significant increase in IFN- γ levels and a significant decrease in IL-10. During the 12-week trial, no severe adverse reactions were noted. Two of 10 patients developed mild nausea, and one patient developed insomnia. Other side effects can include genitourinary symptoms, hematologic abnormalities, and neurologic symptoms. Because MMF is an immunosuppressant agent, there is concern about viral or bacterial infections. Satchell and Barnetson have reported that a patient who was treated with MMF developed staphylococcal septicemia and endocarditis and required a mitral valve repair.⁴⁰ Further studies are needed to document the safety and efficacy of MMF in patients with AD.

Interferon- γ

Interferon gamma is a Th1 cytokine that in vitro suppresses IL-4-mediated IgE production and was theorized to be beneficial in AD. A number of studies demonstrated that recombinant human IFN- γ 1b (rIFN- γ) was effective and safe in the treatment of moderate-to-severe AD.^{5, 14, 41, 45} A large Phase III multicenter, double-blind placebo-controlled trial did not document efficacy in the primary endpoint, namely a change in EASI score.⁹ Improvement in quality-of-life parameters was noted. Because this was only a 12-week trial, a longer intervention period may have been needed. Dosing in this group also may not have been adequate. Ellis et al found that clinical improvement in their patients correlated with reductions in white blood cell counts, eosinophil and lymphocyte counts, and with normalization of the CD4-to-CD8 ratio among lymphocytes.⁸ They believed the efficacy of IFN- γ therapy in AD may depend on these changes. Two open-label studies have suggested improvement with long-term rIFN- γ therapy.^{41, 45} One study attempted

to determine which patients would benefit from IFN- γ therapy.³⁰ Noh and Lee treated 68 patients with rIFN- γ and classified them into three groups based on clinical severity score responses: (1) improvement greater than 20%, (2) improvement less than 20%, and (3) no improvement. Patients showing greatest improvement were found to have blood eosinophil percentages less than 9% and serum IgE levels less than 1500 IU/mL. These investigators also evaluated the use of rIFN- γ in conjunction with hyposensitization to house dust mite in patients with AD. In this small study, they found that the group with hyposensitization and rIFN- γ had the greatest improvement in clinical severity score.³¹

Although studies of skin biopsy lesions have shown that IFN- γ is decreased in acute AD lesions, IFN- γ was found to be elevated in chronic AD skin lesions.¹² A mouse AD model suggested that IFN- γ was important in the lichenification seen in chronic AD.⁴⁴ Further studies are needed to clarify the role of IFN- γ therapy in AD. The expense and inconvenience of injections and laboratory monitoring limit the use and evaluation of IFN- γ .

Intravenous Immunoglobulin

Intravenous immunoglobulin also has been used in severe AD. Intravenous immunoglobulin (IVIg) has anti-inflammatory and immunomodulatory properties and has been used successfully in steroid-resistant asthma.^{25, 39} Jolles et al found that IVIg reduces IL-4 protein expression in AD and reported successful treatment of AD with adjunctive high-dose IVIg.^{18, 19} Huang et al reported that IVIg was safe and effective for severe intractable AD and documented decreases in ICAM-1, ELAM-1, and ECP levels.¹⁶ Wakim et al found no clear clinical benefit in nine patients treated with 2 g/kg per month for seven infusions.⁴⁸ The author has followed a group of young infants who had very severe AD and food allergies who presented with recurrent infections and very low IgG levels. The diagnosis has been transient hypogammaglobulinemia of infancy, and four out of five patients benefited clinically from IVIg.²⁸ This is a very expensive therapy, however, and should be reserved for special cases.

OTHER THERAPIES

Leukotriene Antagonists

Leukotriene antagonists are another possible therapy for AD. Carucci et al reported that four patients with poorly controlled AD improved with zafirlukast therapy.⁷ An open-label pilot study of zileuton 600 mg four times daily for six patients with severe AD also reported improvement in erythema and a trend toward improvement in pruritus.⁵⁰ The other available leukotriene antagonist, montelukast, was studied in a

group of eight adult patients in a double-blind placebo-controlled, cross-over manner for a total of 8 weeks.⁵¹ A small but significant difference in AD scores was found between placebo and active agent. Larger placebo-controlled studies are needed to determine if the leukotriene antagonists are effective for patients with AD.

Probiotics

In young infants with food allergy and AD, probiotics may be a useful therapy. Intestinal colonization with bacteria is important in promoting Th1 responses and IgA production.¹¹ In mice, antigen transport was increased in the absence of intestinal microflora. Initial studies found that *Lactobacillus* GG-derived enzymes suppressed lymphocyte proliferation to bovine caseins and might be beneficial in the down-regulation of hypersensitivity reactions to ingested proteins in patients with food allergy.⁴⁶ The clinical and immunologic effects of the elimination of cow's milk without and with the addition of *Lactobacillus* GG were assessed in infants with AD and food allergy.²⁴ AD improved and fecal levels of alpha-1-antitrypsin decreased in the infants in the probiotics group.

A follow-up randomized, placebo-controlled trial of infants who were weaned to a whey hydrolysate formula with or without probiotics found that after 2 months, a significant improvement in skin condition occurred in patients in the probiotic-supplemented formula in comparison with the control group.¹⁷ In addition to a reduction in the AD score, a reduction in the concentrations of CD4 in the serum and eosinophilic protein X in the urine was seen. Another study showed that probiotics may be helpful in prevention of atopic disease.²⁰ In this double-blind, randomized, placebo-controlled trial, mothers with at least one first-degree atopic relative (or partner) received *Lactobacillus* GG prenatally for 2 to 4 weeks, and their infants received it postnatally for 6 months. The frequency of atopic eczema in the probiotic group was half that of the placebo group. These early trials are promising, although larger multicenter trials are needed.

SUMMARY

New topical immunomodulator therapies (tacrolimus and pimecrolimus) are promising new therapies for AD. They are safe and efficacious and do not have the local nor systemic side effects, which can occur with topical steroids. Other immunomodulatory therapies such as IVIg and IFN- γ may be useful in specific recalcitrant patients. Probiotics offer a potential new therapy for prevention and treatment of AD and food allergy. Other agents being evaluated for asthma including soluble IL-4R and anti-IgE.

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