Atopic Dermatitis:

INSIGHTS, ISSUES (DO CALCINEURIN INHIBITORS CAUSE CANCER?), AND INTEGRATED MANAGEMENT

What Is Atopic Dermatitis?

Pathogenesis of Atopic Dermatitis: Why Does It Happen? What Makes It Worse?

Topical Corticosteroids and Calcineurin Inhibitors: Safety and Efficacy in Children

Perspective on Cancer Risk Associated with Topical Calcineurin Inhibitors

An Integrated Approach to the Long-Term Management of Atopic Dermatitis

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INTRODUCTION

WHAT IS ATOPIC DERMATITIS?

PATHOGENESIS OF ATOPIC DERMATITIS: Why Does It Happen? What Makes It Worse?

TOPICAL CORTICOSTEROIDS AND CALCINEURIN INHIBITORS: SAFETY AND EFFICACY IN CHILDREN

PERSPECTIVE ON CANCER RISK ASSOCIATED WITH TOPICAL CALCINEURIN INHIBITORS

AN INTEGRATED APPROACH TO THE LONG-TERM MANAGEMENT OF ATOPIC DERMATITIS

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Estimated time to complete this educational activity: 2 hours.

Target Audience
This activity has been developed for pediatricians, pediatric nurses, and other health care professionals who are involved in the diagnosis and management of infants and children with atopic dermatitis.

Educational Needs
Atopic dermatitis (AD), the most common type of eczema, can be a chronic, life-altering skin condition. It affects nearly 15 million Americans. In 90% of people, AD develops before age 5. In fact, nearly 20% of school-age children have the disease. In 40% to 60% of these individuals, AD persists beyond puberty and into adulthood. Although there is currently no cure, various interventions exist to control symptoms. This supplement will provide physicians and other health care professionals who care for infants and children with AD a greater understanding of the extent of the clinical problem; the differential diagnosis of AD; the pathogenesis of AD, including the role of allergens and irritants; and the benefits and risks of current topical therapies for AD. In the last article, this supplement will outline an integrated approach to the long-term management of infants and children with AD.

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

- identify the skin lesions that are characteristic of AD and differentiate them from other common skin disorders.
- describe the role of allergens and irritants in AD and help patients/parents understand how to avoid them.
- list the two main classes of topical therapies available for patients with AD and summarize their benefits and risks.
- outline and communicate specific strategies for the long-term management of individual patients with AD.

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Dr Tharp has disclosed that he has received research grants as an investigator from Abbott Laboratories, Astellas Pharma Inc., Biogen Idec Inc., Genentech, Inc., Genmab A/S, and Therakos, Inc. He has also received honoraria as a speaker from Astellas Pharma Inc., Novartis Pharmaceuticals Corporation, and Pfizer Inc. He has also received honoraria for participating in advisory boards from Genentech, Inc., and Novartis Pharmaceuticals Corporation. He has disclosed that he will be discussing unlabeled/unapproved uses of drugs or medical devices.

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topic dermatitis (AD) is a chronic, inflammatory skin disease characterized by the presence of highly pruritic eczematous lesions. Although the disease typically presents and resolves during childhood, a significant number of patients continue to be affected into adulthood. The prevalence of AD is increasing steadily, and with it we are seeing a parallel increase in the prevalence of other atopic diseases. Epidemiological data indicate that at least 50% of all children with AD will go on to develop asthma and/or allergic rhinitis in later life, the so-called “atopic march.” The long-term goal of AD therapy is to employ early intervention strategies directed at the effective control and/or prevention of future flares. An added theoretical benefit, yet unproven, is that good control of AD may also serve to interrupt the “atopic march.”

The purpose of this supplement is to provide the reader with basic knowledge of the pathogenesis, diagnosis, and long-term management of AD. Dr Mary Chang begins with an overview of diagnosis, focusing on the many mimickers that can make identification of AD a challenge. The reader will then gain an appreciation of the complex immunopathogenesis of AD and the role of triggers in the induction and exacerbation of eczema in the article by Dr Mark Boguniewicz. This will be followed by my own discussion of the safety, efficacy, and appropriate use of topical corticosteroids and the newer agents, calcineurin inhibitors (CNIs), in treating AD. I will also present clinical trial data demonstrating the ability of novel dosing schedules to minimize side effects and/or maximize treatment outcomes. Next, Dr Thomas Gross will address the reality behind the fears that prompted the US Food and Drug Administration’s concerns about the potential cancer risk in children using topical CNIs. Finally, Dr Michael Tharp will outline an integrated long-term approach to the treatment of AD, focusing on the use of adjuvant strategies, either alone or in combination with currently available topical therapies, to effectively control the disease. We hope that this supplement will provide health care professionals with practical insights into the management of patients with AD.

What Is Atopic Dermatitis?

Mary W. Chang, MD

Atopic dermatitis (AD) is a chronic, relapsing skin disorder manifested by itchy, dry skin and a characteristic rash that cycles through phases of exacerbations and remissions. Results from epidemiological studies indicate that the prevalence of AD has been increasing steadily over the past 40 years, and the disease now affects 10% to 17% of the people in the United States. Ninety percent of all AD patients are diagnosed before the age of 5 years; the disease improves around puberty in the majority. However, a significant number continue to be affected with AD into adulthood. Although there is currently no cure, AD can be controlled with proper maintenance and treatment strategies. Disease management is directed toward symptom relief, patient/parent education, and the prevention of secondary complications. It is important for parents and children alike to understand that there is no normal skin in an individual with AD—only visibly uninvolved skin.

For the dermatologist, AD is a commonly seen skin disease that accounts for an abundance of patient visits. The pruritus associated with the disease can be so severe that it has a significant negative impact on patients’ quality of life, particularly in those with moderate-to-severe disease. AD can lower self-esteem, negatively affect school performance and social interactions, disrupt sleep, and heighten the day-to-day stress experienced by both patients and their families.

Repeated and prolonged scratching of AD lesions produces secondary skin changes such as excoriation, breakdown of the skin barrier, lichenification (thickening of the skin due to prolonged scratching), and pigmenary changes. For this reason, AD is referred to as the “itch that rashes” rather than the “rash that itches.” In infants and young children, AD lesions are typically found on the scalp, face, and extensor surfaces of the extremities (Figure 1 on page 5). Pruritus, although present, is not always obvious in infants. Rubbing against bed sheets or a parent’s shoulder are clues. Fussiness and poor sleep are
also signs of pruritus. Older children and adults are more often affected by AD on the neck, wrists, ankles, and flexural surfaces (Figure 2). Although it is not known why the distribution of AD changes with age, it can be a valuable diagnostic tool.

**Diagnosis of AD**

The diagnosis of AD can be challenging since the type and appearance of the skin lesions on any individual will vary according to the degree of inflammation, stage of healing, frequency of scratching, and presence/absence of secondary infection. The primary diagnostic criteria of AD include pruritus, lichenification, a history of a chronic relapsing course, and a personal or family history of atopy.

The numerous minor criteria, or soft signs, can also aid diagnosis of AD. For example, xerosis or dry skin is an important soft sign of AD. Since dry skin cannot hold moisture, it tends to fissure. These disruptions in the skin barrier increase the susceptibility to irritation and infection. In babies with widespread facial AD, there is often a striking sparing of the nose and mouth area that can aid diagnosis (Figure 1). Wool intolerance is a soft sign of AD. Since dry skin cannot hold moisture, it tends to fissure. These disruptions in the skin barrier increase the susceptibility to irritation and infection.

**Other Forms of Eczematous Dermatitis**

Since the skin lesions of AD can manifest as papules, vesicles, plaques, nodules, and excoriations, they can easily be confused with other forms of eczematous dermatitis. The final diagnosis is made on the basis of a careful history, observations from a keen eye, and the use of laboratory tests to confirm or exclude other disorders when the diagnosis is unclear.

*Contact dermatitis* occurs when the skin comes into contact with an external causative agent. This diagnosis should be considered when eczematous patches and plaques are seen on discrete, localized regions of the body. Ideally, a positive exposure history can be elicited.

**Figure 3** shows a classic example of *pityriasis rosea* on the trunk of a teenager. The first lesion to develop, known as the herald patch, can be seen below as an oval-shaped erythematous patch covered with fine scales often in a ring-shaped distribution. Later lesions resemble the primary plaque and follow the same lines but are smaller.

*Psoriasis* is a chronic disease characterized by increased epidermal proliferation. The high cell turnover rate results in the production of plaques covered with white or silvery micaceous scales that are thicker than those seen in AD (Figure 4 on page 6). Although there is erythema, there is typically no annularity, lichenification, or eczematous dermatitis.

*Perioral dermatitis* or *periorificial dermatitis* is an irritant reaction to a nonspecific agent that manifests as clusters of pink papules around the mouth. This condition should be treated with rosacea-type medications, such as oral erythromycin or a topical metronidazole preparation. Topical corticosteroids are contraindicated.

*Scabies* is an intensely pruritic infestation that typically occurs on the trunk, extremities, and between the fingers. In infants, this diagnosis is often missed, leading to prolonged infestation. Extensive eruptions, either as nonspecific red papules all over the body or as very thick crusty scales (Norwegian or crusted scabies), can occur. Scabies can be easily confused with AD, however, and a positive skin scraping for *Sarcoptes scabiei* will confirm the diagnosis.2

*Infantile seborrheic dermatitis* (ie, cradle cap) presents as yellow, greasy scales on the scalp about 1 week after birth. It is usually not itchy and is a harmless condition that babies usually outgrow.

*Nummular dermatitis* is characterized by coin-shaped, eczematous patches and plaques that arise symmetrically on the backs of hands, feet, forearms, and legs. Although it can be itchy, *nummular dermatitis* is usually less pruritic than classic AD. The fact that there is no central clearing or annularity to the lesion distinguishes it from a fungal infection.
Fungal Infections

*Mycosis fungoides* is a serious, albeit rare, form of cutaneous T-cell lymphoma in children. Initially, the lymphoma manifests as a cutaneous lesion closely resembling that seen in patients with AD. With time, however, the patches of infiltrated skin take on their classic appearance and show a tendency for central clearing or an arciform/poly-cyclic arrangement. When suspicions arise, a biopsy specimen should be taken to confirm the diagnosis.²

Fungal infections may produce very itchy seborrheic-like scaling of the scalp with or without alopecia (*tinea capitis*) or annular, scaling patches with erythema on the trunk and extremities (*tinea corporis*), or on the face (*tinea faciei*).³ Each of these can mimic AD lesions in certain stages of development. The use of topical steroids is contraindicated, and an antifungal agent, such as oral griseofulvin, should be prescribed. Physicians and parents should be aware of the fact that during the first week of treatment with oral griseofulvin, patients with tinea capitis may develop a secondary rash over their body that is mildly pruritic. This is called an id reaction and is not a drug allergy.

The child in Figure 5 had a chronic rash that was misdiagnosed as AD and treated with a topical corticosteroid. Although the condition improved initially, it later worsened. The eczematous patch seen on the girl's face is a bit puzzling, but upon close inspection one can see that the lesion has an erythematous rim with an annular, ring-shaped appearance. This child has *tinea incognito*. Although the topical steroid decreased inflammation and scale formation, thus improving the rash initially, the fungus continued to proliferate and, in doing so, produced the peculiar lesion pattern.

When dealing with suspected fungal infections, it is best to err on the side of caution. If the lesion is red and scaly, or eczematous and puzzling, scrape the area and have laboratory tests performed with a potassium hydroxide preparation for dermatophytes and a fungal culture.

Complications of AD

Secondary skin infection is a common complication seen in patients with AD. Children with AD have higher colonization of staphylococci. Repeated scratching breaks the skin barrier, thus increasing the probability that a bacterial (*Staphylococcus aureus, Streptococcus pyogenes*), fungal, or viral infection will invade the tissue. Infections spread rapidly across AD skin. When AD becomes acutely infected with gram-positive cocci, there is more swelling of the affected area, and the yellow crusts that are characteristic of impetigo are visible. *Eczema herpeticum* manifests as an explosive vesicular eruption that spreads like wildfire across AD skin.⁴ The patient with eczema herpeticum will always be at risk for recrudescence of herpes simplex. *Molluscum contagiosum*, caused by a poxvirus, typically produces a benign self-limited papular eruption.⁴ However, in patients with AD, who are generally more prone to the disease, it can cause disseminated and recalcitrant eruptions. It is important to remember to treat the AD before treating the molluscum.

Conclusion

In conclusion, AD is a chronic inflammatory skin disease that affects both children and adults. Although the diagnosis is typically straightforward for the experienced physician, it must be differentiated from a number of other eczematous conditions. Secondary infections frequently become superimposed on AD lesions, thus complicating the diagnosis and treatment of the disease.

References

Pathogenesis of Atopic Dermatitis: Why Does It Happen? What Makes It Worse?

MARK BOGUNIEWICZ, MD

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by cutaneous hyperreactivity. Multiple factors, including transepidermal evaporative losses and epidermal lipid abnormalities, interact to heighten skin reactivity in AD patients by damaging the permeability barrier and increasing the susceptibility of the stratum corneum to colonization by Staphylococcus aureus. Although skin barrier function and inflammatory signaling are linked defensive functions of the epidermis, and minimal barrier perturbations can trigger cutaneous immune phenomena, there has been ongoing discussion as to which comes first. Does the primary pathology of AD originate in the epidermis and then trigger secondary immune responses in the skin barrier, or is the primary pathology an immune dysfunction that subsequently orchestrates the skin abnormalities? This paper will discuss aspects of the complex immunopathogenesis of AD (Figure) and then briefly touch upon the role of calcineurin inhibitors (CNIs) as immunomodulators of AD pathology.

Pathology of AD

There is now abundant evidence linking AD with systemic immune dysregulation. Upregulation of various interleukins, persistent monocyte activation, increased eosinophil infiltration, and elevated serum immunoglobulin E (IgE) levels are all immune abnormalities that can be measured in AD patients. The fact that the number of IgE(+) Langerhans’ cells (LCs) is greater in patients with active AD and asthma than in those with inactive disease suggests that atopic diseases may share a common systemic regulatory mechanism. Of note, more than half of all children with AD go on to develop asthma and allergic rhinitis in a process termed the “atopic march.”

As clinicians, we recognize that there is often no linear flow from the pathology of uninvolved skin to that of acutely and chronically inflamed skin. Instead, things are much more complex—patients with AD will develop acute exacerbations on top of chronic lesions and so forth. Evidence suggests that the key players in the inflammatory response change as it progresses from an acute to chronic stage. Whereas acute lesions are predominantly associated with increased interleukin (IL)-4 and IL-13 expression, chronic inflammation is associated more with eosinophilia and increased IL-5, IL-12, and gamma interferon expression. In addition, there is more upregulation of IgE receptors and inflammatory dendritic epidermal cells (IDECs) in exemidus lesions. LCs are important immunosurveillance cells that express high-affinity receptor sites for IgE molecules in atopic individuals. Hence, they are capable of capturing and presenting allergens to T cells in a much more efficient way than antigen-presenting cells that lack IgE receptors. IDECs, on the other hand, are more aberrant immune cells that appear to contribute to the chronic inflammation seen in persistent skin lesions.

Along with our increased understanding of the immunopathology of cutaneous inflammation, there has been an ongoing search for disease-specific biochemical markers to facilitate the differential diagnosis of AD. Recent data suggest that two cytokines—thymus and activation-regulated chemokine and cutaneous T-cell-attracting chemokine—may be specific markers for AD. Both of these are clearly elevated in the serum of patients with AD compared to that of patients with other atopic diseases, such as asthma and allergic rhinitis, and show a strong positive correlation with disease severity. Most importantly, serum levels of both of these chemokines decrease dramatically during successful treatment.

Aggravating Factors

Multiple triggers have been shown to induce and exacerbate cutaneous inflammation in patients with AD. In general, AD skin has a lower threshold of responsiveness and is therefore hyper-reactive to irritants and allergens. Subsets of susceptible patients have been shown to have elevated levels of allergen-specific IgE antibodies and T cells expressing cutaneous lymphocyte-associated antigen (CLA) homing receptors on their surface. Significant clinical
improvement in the eczema may occur when environmental control measures are initiated in patients with proven allergies.

Food allergies may be implicated in approximately one third of pediatric patients with moderate-to-severe eczema, primarily those under 5 years of age. Like aeroallergens, food-specific T cells expressing CLA can be found in the skin of susceptible AD patients. To identify a suspected food allergy, physicians must pay close attention to the patient's history of food-related AD and select appropriate tests to confirm their suspicions. Ninety percent of all food allergies associated with AD are due to seven food proteins (milk, egg, peanut, soy, wheat, fish, and nut proteins). Although oral food challenges are commonly used to confirm allergens, test results can be misleading. Single food challenges usually induce only a transient skin rash, whereas repeated challenges, more typical of real-life exposure, result in eczematous lesions that are identical to those of the natural disease. Epicutaneous skin tests, on the other hand, are best used to rule out food allergies since their negative predictive value (~95%) far exceeds their positive predictive value (~50%).

The in vitro Pharmacia ImmunoCAP assay (Pharmacia, Uppsala, Sweden), a technique used to quantify blood concentrations of allergen-specific IgE, is another tool that physicians can use to identify patients who may react to a subsequent food challenge. Thus far, specific IgE levels correlating with a 95% chance of a clinical reaction have been defined for four of the seven major allergens—milk, eggs, peanuts, and fish. However, the test does not predict what type of reaction the patient will have, its intensity, or whether the allergy is related to the patient's skin disease. Importantly, low food-specific IgE values do not rule out the possibility of a clinically important reaction. In general, if a patient’s IgE levels are above the 95% cutoff, we defer the food challenges and recheck the patient’s specific IgE in 6 to 12 months. If the levels drop below 2kUA/L, then we consider challenging the patient’s specific IgE in 6 to 12 days.

Topical CNI therapy is also associated with significant reduction of S. aureus on the skin of patients with AD.

—Boguniewicz

Recent studies have identified a deficiency in the secretion of antimicrobial peptides by keratinocytes in the skin of patients with AD, making them more susceptible to colonization and infection by a number of microbes. This is not a primary defect, but rather results from increased levels of T-helper subset 2 cytokines and inhibiting T-cell activation. In conclusion, the prevalence of AD has increased, and more than half of children with AD will go on to develop asthma or allergic rhinitis. As our understanding of the complex immunopathogenesis of this disease unfolds, more effective targeted therapies may be developed with the potential to interrupt this “atopic march.”

References
Topical corticosteroids and Calcineurin Inhibitors: Safety and Efficacy in Children

Seth J. Orlow, MD, PhD

Topical corticosteroids are highly useful in the short-term control of atopic dermatitis (AD). These agents have been shown to reduce inflammation rapidly and effectively by attenuating T-cell activation and the subsequent upregulation of early cytokines.1,2 There are seven potency classes, ranging from superpotent class 1 corticosteroids, such as betamethasone and clobetasol, to the least potent, class 7, topical hydrocortisones.3 Safety concerns are primarily about the more potent topical steroids or those with low- to mid-potency that are used for long periods of time or over large areas of the body in young children. Survey data from 200 outpatients with AD or parents of children with AD revealed that 73% were concerned about the safety of topical corticosteroids and up to 36% were non-compliant because of their concerns.4 Patient/parental concerns included skin thinning (35%) and systemic absorption, including effects on growth and development (10%). Clinical trial results have demonstrated the reality behind these fears. Topical application of betamethasone BID for 2 to 3 weeks reportedly produced measurable adrenal suppression in 23% to 28% of infants and children who had AD on 40% to 45% of their total body surface area.5 A similar suppression was seen in 40% to 47% of adolescents treated with betamethasone-clotrimazole cream BID for tinea pedis or tinea cruris for 2 to 4 weeks.6 Consequently, this combination cream is no longer approved for use in patients younger than 17 years of age.

Topical Corticosteroids

Short-term clinical trials have demonstrated that topical corticosteroids can be used effectively to gain rapid control of AD.7 Most corticosteroids, however, are not approved for use in children younger than 2 years of age or for long-term use in either pediatric or adult patients. Fluticasone cream is an exception to this rule and has US Food and Drug Administration (FDA) approval for short-term use in pediatric patients 3 months of age or older. Recent results from a 16-week clinical trial indicate that twice-weekly fluticasone maintenance therapy is a safe and effective way to achieve long-term control of moderate-to-severe AD in adolescents and adults.8 Specifically, patients treated with intermittent fluticasone, cream (0.05%) or ointment (0.005%), were 5.8 and 1.9 times less likely to flare, respectively, than those treated with vehicle. Importantly, there were no signs of skin atrophy or adrenal suppression reported.

Calcineurin Inhibitors

Topical calcineurin inhibitors (CNIs) are nonsteroidal agents that have been shown to reduce inflammation by blocking specific steps involved in T-cell activation.9 Thus far, two have been approved for short-term and intermittent long-term use in pediatric patients with AD: tacrolimus ointment (0.03%) and pimecrolimus cream (1%).10,11 The CNIs are the most intensively studied class of topical agents. Multiple short-term and long-term clinical trials have assessed the effects of pimecrolimus in nearly 21,000 patients, including 7,000 children and 3,000 infants. Similar numbers have been reported for tacrolimus. The results of these studies have demonstrated a clear efficacy advantage of each CNI over vehicle. Representative data from one 6-week clinical trial with pimecrolimus cream demonstrated significant overall improvement, including specific improvement on the face and neck areas, of infants and children with mild-to-moderate AD (Figure 1).12 An additional report provides representative data demonstrating the effectiveness of tacrolimus ointment in children with moderate-to-severe AD.13 As shown in Figure 2 on page 10, three quarters of the patients treated with tacrolimus ointment (0.03% or 0.1%) experienced at least a 50% improvement in their eczema after 12 weeks of treatment in comparison to only one quarter of those treated with vehicle. Equally as impressive was the observation that four to five times more patients treated with tacrolimus experienced 100% clearing of their eczema. The benefits of early intervention with pimecrolimus were demonstrated in a long-term clinical trial that enrolled infants, children, and adults with mild-to-severe AD.14 Study results showed that twice as many patients in each age group, who applied pimecrolimus cream BID at the first sign of skin inflammation, completed the 6-month study with no subsequent flares.

Figure 1. Significant Overall Improvement and Improvement in the Face and Neck Areas During 6-Week Pimecrolimus Therapy Versus Vehicle Only in Infants and Children (N=403) With Mild-to-Moderate AD

<table>
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<th>Days</th>
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AD = atopic dermatitis; EASI = Eczema Area and Severity Index.

*P<0.05 vs vehicle, †P<0.01 vs vehicle, ‡P<0.001 vs vehicle, 8Day 8: first scheduled visit.

Source: Eichenfield LF et al.12

Figure 2. All body and Face/neck data demonstrating the effectiveness of tacrolimus ointment in children with moderate-to-severe AD.
Early intervention with pimecrolimus also significantly increased the time to first flare (55 versus 22 days) and time between subsequent flares (44 versus 26 days) in comparison to placebo.¹¹

Long-term follow-up of 408 adults and 391 children treated with tacrolimus ointment 0.1% for up to 4 years revealed that total body surface area involvement and Eczema Area and Severity Index (EASI) scores declined steadily during the first 24 months of treatment and then remained down to study end point.¹² Similar findings were observed in a 2-year follow-up study of infants (3 to 24 months) treated with pimecrolimus cream.¹³ Infants reportedly achieved a 70% reduction in EASI score after 3 months of therapy and then maintained this level until study end point.

Unlike the topical corticosteroids, the CNIs do not cause skin atrophy, telangiectasia, acne, perioral dermatitis, adrenal suppression, growth retardation, cataracts, or glaucoma.¹⁴ Patients may, however, experience stinging and burning at the site of application when using a topical CNI, particularly if their eczema is severe. The incidence of this side effect decreases substantially if the eczema is first brought under control with a topical steroid. Although 12-week studies have demonstrated small increases in the instances of herpes and folliculitis in patients using tacrolimus in comparison to placebo, long-term studies have failed to replicate these findings in either tacrolimus or pimecrolimus users.⁵,⁶ Currently, there is also no evidence that the topical CNIs increase susceptibility to serious systemic infections or interfere with systemic immune responses.²,⁷,⁸ Pharmacokinetic data indicate that serum drug concentrations are usually undetectable in patients using topical CNIs and that there is no systemic accumulation, even during prolonged exposure.⁹,¹⁰ Children undergoing long-term treatment with these agents display normal antibody titers and B-cell–dependent vaccination responses and show no evidence of delayed-type hypersensitivity following routine inoculations.¹¹

Regulatory Actions

Despite clinical data attesting to the long-term safety and efficacy of topical CNIs, there has been growing concern over the increased use of these agents in infants and children with AD. In February of 2005, the Pediatric Advisory Committee of the FDA recommended measures to emphasize to physicians and patients that:²

- Animals exposed to CNIs can develop malignancy.
- Topical CNIs are not indicated for use in children less than 2 years of age.
- Topical CNIs are indicated for short-term and intermittent long-term use.
- Topical CNIs are indicated for patients who do not respond to or should not be treated with other agents.
- The committee recommends the addition of “black box” warnings of potential cancer risk to all topical CNIs and the development of medication guidelines.

One month later in a Public Health Alert, the FDA reiterated these recommendations and announced its intent to add “black box” warnings of potential cancer risk to the labeling of each agent.¹² On January 19, the FDA approved updated labeling for pimecrolimus and tacrolimus that include a boxed warning that acknowledges that no causal link has been established between topical CNIs and reported cases of cancer but nonetheless notes “concern about a potential risk.”¹³

Conclusion

In summary, although topical corticosteroids are clearly effective for the short-term control of AD, potentially serious side effects and the lack of long-term safety data limit their use in pediatrics. In contrast, numerous studies and clinical experience with over 8 million patients globally have demonstrated that the topical CNIs are safe and effective for both the short-term control and long-term maintenance of AD. Multiple, large-scale clinical trials are continuing to amass safety and efficacy data in infants and children using these agents for 2, 3, even 5 years and longer.

References

6. Protopic® (tacrolimus) Ointment 0.03% and 0.1% [package insert]. Deerfield, Ill.: Astellas Pharma US, Inc.; 2006.

Figure 2. Cumulative Percentage of Children (N=351; Mean Affected Body Surface Area, 47.7%) Experiencing Moderate, Marked, Excellent, or 100% Improvement in Their Eczema Following 12 Weeks of Therapy With Either 0.03% or 0.1% Tacrolimus Ointment or Vehicle

<table>
<thead>
<tr>
<th>% Patients</th>
<th>Vehicle</th>
<th>0.03%</th>
<th>0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>26.7%</td>
<td>72.6%*</td>
<td>78%*</td>
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*P<0.001 versus vehicle.

Source: Paller A et al. Figure reproduced with permission from the Journal of the American Academy of Dermatology.
The US Food and Drug Administration (FDA) has voiced concern over the dramatic increase in the use of topical calcineurin inhibitors (CNIs) as first-line therapy for atopic dermatitis (AD), particularly in children under 2 years of age. Systemically administered CNIs are known to increase the incidence of both lymphoma and skin cancer in pediatric organ transplant recipients, with a median latency of 1 to 2 years and 10 years, respectively (data derived from analysis of the Israel Penn International Transplant Tumor Registry [IPITTR]).

Since ultra–long-term safety data will not be available for the topical CNIs for many years, the FDA has required the addition of a boxed warning to the labeling of pimecrolimus and tacrolimus because of the potential cancer risk. This paper will review the cancer risk in both patient and animal populations.

Cancer Incidence With Immunosuppression

To date, the IPITTR has documented 363 cases of cancer in children who have received organ transplants. Statistical summaries indicate that posttransplant lymphoproliferative disease (PTLD) or lymphoma was reported in 80% of the cases, and skin cancer was reported in 12%. Interestingly, the incidence of melanoma, a type of skin cancer that is more prevalent in immunocompromised individuals, was only 0.6% in these children. PTLDs typically occurred within 1 to 2 years, and skin cancers occurred anywhere from 4 to 40 years posttransplant (median, 10 years).

It is the high incidence and rapid rate of development of PTLD that physicians are most concerned about when giving chronic immunosuppression to children after organ transplantation. Whereas 5 to 10 of every 100 pediatric patients receiving immunotherapy will develop PTLD, lymphoma is seen in only 1 out of every 10,000 children in the general population. This is a 1,000-fold difference.

Epidemiological data indicate that the risk of skin cancer increases as a function of time up to 30 and 40 years posttransplant, suggesting that there is a dose-dependent relationship between immunosuppression and risk. Compared with age-matched controls in the general population, transplant recipients have a four- to fivefold increase in the risk of skin cancer.

An in-depth analysis of the treatment histories of 20,000 patients in the IPITTR who developed cancer after transplantation revealed that there was no single agent that put patients at risk for developing cancer. Rather, risk varied directly with the cumulative dose or exposure to chronic immunosuppression. This will be a critical factor when evaluating the safety of topical CNIs.

Pharmacokinetic studies have shown that systemic exposure to topically applied CNIs is very small. Pooled clinical data indicate that the highest systemic exposures ever observed in pediatric patients who were treated twice daily with tacrolimus ointment 0.03% for 3 to 12 weeks: 87% had whole blood levels of less than 0.5 ng/mL, 12% had levels between 0.5 and 1.0 ng/mL, and 1% had levels between 1.0 and 2.0 ng/mL.

Putting this into perspective, voluntary reports indicate there have been only 25 instances of malignancies in 5 million users of topical pimecrolimus, and only three of these have occurred in children: 7 skin tumors, 13 lymphomas (three in children <3 years old), and 5 miscellaneous types of cancer. Similarly, there have been 31 reported cases of cancer in patients using tacrolimus ointment, out of a total of 1.7 million users: 14 lymphomas (eight noncutaneous and six cutaneous T-cell lymphomas) and 17 nonmelanoma skin cancers (NMSCs). None of these malignancies occurred in children under the age of 16 years. Based on the tumor histology and time course of development in each affected patient, no evidence was found to suggest that the topical agents were a causative factor in the etiology of these lymphomas. Lymphomas of this type are often misdiagnosed in their early stages of development, and in many of these cases it was unclear whether the patient did or did not have the lymphoma before they

ATOPIC DERMATITIS: INSIGHTS, ISSUES, AND INTEGRATED MANAGEMENT

PERSPECTIVE ON CANCER RISK ASSOCIATED WITH TOPICAL CALCINEURIN INHIBITORS

THOMAS G. GROSS, MD, PhD

Pharmacokinetic studies have shown that systemic exposure to topically applied CNIs is very small.

Gross

Carcinogenicity Data and Perspective

The FDA’s concern about the potential cancer risk of topical CNIs is based on both preclinical and clinical data. Although rodent carcinogenicity studies have demonstrated an increased incidence of lymphoma with both topically applied pimecrolimus and tacrolimus, the malignancies occurred only when the drugs were dissolved in ethanol vehicle at doses that were 26 to 47 times the maximum recommended human dose (MRHD). Topical pimecrolimus cream 0.2%, applied at a dosage of 2 mg/kg per day for 2 years (1.5 times the MRHD), has also been shown to increase the incidence of follicular cell adenoma of the thyroid in mice compared with placebo controls. Pharmacokinetic studies have shown that systemic exposure to topically applied CNIs is very small. Pooled clinical data indicate that the highest systemic exposures ever observed in an adult or child treated with pimecrolimus cream (1%) were only 23 ng/mL and 38 ng/mL, respectively. Whole blood samples taken from 75 children treated with twice-daily pimecrolimus cream (1%) on up to 92% of their total body surface area for 3 weeks (five children were treated up to 1 year) revealed average drug concentrations of less than 0.5 ng/mL in 67% of the samples and less than 2.0 ng/mL in 97% of the samples. A similar low level of systemic exposure has been reported in pediatric patients who were treated twice daily with tacrolimus ointment 0.03% for 3 to 12 weeks: 87% had whole blood levels of less than 0.5 ng/mL, 12% had levels between 0.5 and 1.0 ng/mL, and 1% had levels between 1.0 and 2.0 ng/mL.

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started using the CNI. When these data are compared to the expected incidences of lymphoma (22/100,000) and NMSC (533/100,000) in the general population, voluntary reports indicate that the frequency of lymphoma and NMSC in tacrolimus and pimecrolimus users is about 10 times and 100 times less than would be expected.1,3 It is important to remember that these postmarketing data are based on voluntary reports and are therefore not true incidence rates. Nonetheless, they suggest that there is no increase in the incidence of cancer in users of topical CNIs.

Summary and Conclusion

The figure compares daily and cumulative drug exposure in patients with AD, organ transplant recipients with PTLD, and a toxicokinetic cohort of mice during tacrolimus therapy.11 As shown, the cumulative exposure observed in the transplant patients and the cohort of mice, both of which showed an increase in the incidence of lymphoma, were 65,000 and 80,000 ng·hr/mL, respectively, after 122 days of therapy. It is important to note that although the mice were treated with the drug topically, their exposure levels were similar to those of the organ transplant patients who received the drug systemically. In comparison, the cumulative exposure in AD patients was only about 1,400 ng·hr/mL, a level approximately 50-fold less than that observed in the other two groups. Considering the low level of exposure observed in AD patients treated with topical CNIs, do they really have a heightened risk of cancer? At this time, the answer appears to be no. There is limited clinical evidence that the use of topical CNIs increases the risk of malignancies in children or adults. Safety monitoring programs are in progress, however, to continually update our databases and extend them to include ultra long-term users of these agents.

References


TOPOCAL CORTICOSTEROIDS AND CALCINEURIN INHIBITORS: SAFETY AND EFFICACY IN CHILDREN

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12 ATOPIC DERMATITIS: INSIGHTS, ISSUES, AND INTEGRATED MANAGEMENT
AN INTEGRATED APPROACH TO THE LONG-TERM MANAGEMENT OF ATOPIC DERMATITIS

MICHAEL D. THARP, MD

Atopic skin is characteristically dry and unable to hold moisture because of structural and functional abnormalities in the skin barrier that promote transepidermal water loss.1 Dry skin is more likely to crack and split, creating a portal of entry for irritants, allergens, and microbial agents that may induce or exacerbate atopic dermatitis (AD) flares in susceptible individuals. An effective treatment plan for the management of AD begins with avoidance of potential environmental irritants and allergens. Contact irritants, such as detergents, nickel, harsh soaps, and rough fabrics (wool, nylon), may cause local irritation and inflammation, as may sweat and extreme fluctuations in temperature or humidity. Aeroallergens, such as animal dander and dust mites, and food allergens may also exacerbate AD by inducing local or systemic allergic reactions.2 Emotional stress is another potent trigger that may induce AD flares. Good control of AD begins with the avoidance of these potential environmental triggers.

Preventative Skin Care

Hydration of the stratum corneum and the use of occlusive emollients provide the foundation for good skin care in patients with AD. Bathing removes surface allergens and irritants, cleans and debrides the skin, rehydrates the stratum corneum, and relieves stress. This, alone, may significantly reduce irritation and even some of the itch that is associated with the disease. Trapping water on the surface of the skin by applying an emollient immediately after bathing improves the stratum corneum integrity and significantly decreases pruritus.3 Ointments are most effective for trapping water on the surface of the skin, followed by creams, lotions, and gels, which are the least occlusive of all.

Choice of cleanser is also a critical issue for AD patients because their skin is easily irritated.2 The degree of harshness or mildness of a cleanser is determined by its surfactants—which are responsible for its cleaning power—and by its pH. Classic soaps, such as Irish Spring® and Ivory®, contain natural surfactants that tend to be harsh on AD skin. Synthetic detergent (syndet) bar cleansers that contain synthetic surfactants derived from oils, fats, or petroleum products are less drying and cause less barrier disruption than classic, superfatted, transparent, or combination soaps (Figure 1).4 Both Dove® and Olay® have been shown to cause approximately half as much transepidermal water loss as classic soaps, such as Irish Spring, Zest®, Ivory, and Nivea®.5 Body washes can also be classified as harsh or mild based on their surfactants, pH, and emollient content. The potential advantage of body washes is that they can contain more emollients than conventional bar cleansers, so that when a person steps out of the bath he or she already has a film of emollient on the skin surface. It is important to recognize, however, that not all body washes are the same and some that contain natural surfactants can be drying and irritating to the skin of an AD patient.

Therapeutic Options

Although topical corticosteroids can be used effectively to gain rapid control of AD flares, pediatricians are sometimes reluctant to prescribe these agents to infants and children because of potential local and systemic side effects. Recent clinical trial data, however, have shown that twice-daily treatment with fluticasone propionate cream 0.05% is safe in children 3 months to nearly 6 years of age with 62% to 67% AD skin involvement.4 There were no reports of skin atrophy, pigmentedary changes, or adrenal suppression during the 3- to 4-week treatment period. Only five adverse events were recorded: burning and urticaria (one), erythematous rash (one), and telangiectasia (three). Additional findings suggest that intermittent dosing schedules may provide a safer alternative for patients of all ages who require long-term topical corticosteroid therapy.

In a study conducted by Hanifin and colleagues in 2002,6 infants, children, and adults with AD were stabilized with daily fluticasone treatment and then randomized to receive twice-weekly maintenance therapy with either fluticasone or vehicle cream for 16 weeks. The results revealed that patients treated with intermittent fluticasone were seven to eight times less likely to relapse than those treated with vehicle. Importantly, twice-weekly fluticasone use was not associated with skin atrophy or increases in the incidence of skin infections or the use of antibiotics. These latter two observations are particularly important, given the fact that AD skin is colonized with Staphylococcus aureus and more than half of the patient population cultures positive for S. aureus-producing...
Case Study: 7-month-old girl
- Moderate-to-severe eczema on face, trunk, and extremities
- Disease flares regularly
- Parents are anxious and exhausted
- Disease flares regularly
- Parents are using emollients, but they find them time consuming and not very effective

How would you treat this patient?
- Topical corticosteroid for initial disease control and then for maintenance
- Topical corticosteroid for initial disease control followed by a topical CNI for maintenance and perhaps consider an oral antibiotic
- Oral antibiotics alone for initial disease control followed by a topical corticosteroid for flares
- Oral corticosteroids and emollients

Case Outcome
- Initial disease controlled with fluticasone cream 0.05% (2 weeks), oral cephalexin (1 week)
- Patient cleared
- Maintenance therapy
  - Emollients, irritant avoidance
  - Pimecrolimus* (4 weeks), then as needed
  - Alternative Rx
    - Tacrolimus ointment*
    - Intermittent fluticasone*

CNI = calcineurin inhibitor
*Off-label use.

Evolving Approach to Management

Historically, physicians have used a reactive approach to the management of AD. Lower potency steroids are prescribed for minor flares and higher potency steroids for major flares, the goal being to get the eczema under control before the next flare cycle begins. With the advent of topical calcineurin inhibitors (CNIs) came the realization that early intervention of the treatment of AD with these agents could prevent major flares. The impetus for this change came from clinical data demonstrating that the early treatment of AD with pimecrolimus cream effectively aborted flares. Specifically, study results revealed that 68% of infants, 61% of children, and 45% of adults who received intervention treatment with pimecrolimus cream at the first sign or symptom of eczema had zero flares during the 6-month assessment period compared to 30%, 34%, and 19% of those who were treated with vehicle cream, respectively (all P<0.001). In addition, two thirds of the children and adolescents in the pimecrolimus group required no topical corticosteroids compared to 38% of vehicle controls. It is important to point out that the control group avoided the use of corticosteroid rescue medication just by using good bathing techniques and frequent emollient applications.

Another large, randomized trial demonstrated the superiority of tacrolimus ointment (0.1%) over two variants of hydrocortisone ointment in the treatment of adults with moderate-to-severe AD (N=972). After 1 month of therapy, nearly three quarters of the patients in the tacrolimus group had achieved at least a 60% improvement in their eczema compared to half of the patients in the active control group. These group differences were maintained until study end point 5 months later, thus demonstrating the long-term efficacy advantage of tacrolimus ointment over the hydrocortisones.

Action Plan

In summary, an action plan for the treatment of AD begins with good basic skin care, making sure the patient uses a mild cleanser daily and applies an ointment or cream emollient to wet skin after bathing. The avoidance of known irritants and allergens, the use of antihistamines for their sedative effects, and the early intervention of the signs and symptoms of AD with a topical CNI serve as the basis for long-term management (Figure 2). When patients experience severe flares, higher potency topical corticosteroids should be considered along with oral antibiotics. After gaining control of the eczema, the goal is to transition the patient to emollients and intermittent topical CNI maintenance therapy.

References
Atopic Dermatitis: Insights, Issues (Do Calcineurin Inhibitors Cause Cancer?), and Integrated Management
CME Post-Test and Evaluation

Release Date: March 2006  Expiration Date: March 31, 2007  Estimated Time to Complete This Activity: 2 hours

CONTINUING EDUCATION INSTRUCTIONS: There is no fee to participate in this activity.
Please forward the Test Answer Sheet and Evaluation form to:
Center for Advanced Medical Education, 201 South Main Street, Suite 6, Lambertville NJ 08530 FAX (609) 397-5177
Responses for AMA/Physician's Recognition Award credit must be submitted by March 31, 2007.

Instructions: For each of the following questions, circle the single most appropriate answer for each question.
1. Atopic dermatitis (AD):
   a. is typically first diagnosed in children before the age of 5 years.
   b. is the number 1 cause of chronic skin problems in children.
   c. continues to affect a significant number of patients in adulthood.
   d. all of the above

2. The major criteria used to diagnose atopic dermatitis include:
   a. pruritus and lichenification.
   b. a history of a chronic relapsing course.
   c. a personal or parental history of atopy.
   d. all of the above

3. Which of the following is (are) true?
   a. AD is a complex disease with multiple immunopathologies.
   b. There is no evidence of systemic immune dysregulation in AD.
   c. a number of resident and infiltrating cells and cytokines are involved in the evolution of acute to chronic lesions in AD.
   d. a and c

4. AD skin:
   a. is hyperresponsive to irritants and allergens.
   b. is uniquely colonized by high numbers of S. aureus.
   c. has a high number of IgE(+) Langerhans' cells.
   d. all of the above

5. The advantage(s) of therapy with topical CNIs are:
   a. they are safe and effective for long-term use.
   b. they do not cause skin atrophy, increase susceptibility to infection, or affect systemic immune responses after routine vaccination.
   c. serum drug concentrations do not accumulate, even during prolonged exposure.
   d. all of the above

6. The benefit(s) of early intervention with pimecrolimus cream at the first sign of skin inflammation include:
   a. prevention of subsequent flare reactions in patients of all ages.
   b. reduction in the time to first flare.
   c. an increase in the time to first flare and time between subsequent flares.
   d. a and c

7. Which of the following statements are true?
   a. The systemic exposure to topical CNIs is very small.
   b. The frequency of lymphoma and NMSC in patients using topical CNIs is very small compared to the total number of patients who have used these agents.
   c. all of the above
   d. none of the above

8. In-depth analysis of the treatment histories of 20,000 patients who developed cancer after transplantation revealed that:
   a. cancer risk varied directly with the cumulative dose or exposure to chronic immunosuppression.
   b. cancer risk varied inversely with cumulative exposure to chronic immunosuppression.
   c. there was no single agent that put patients at risk for developing cancer.
   d. both a and c

9. Syndet bars and body washes are generally milder and cause less skin barrier disruption and transepidermal water loss than classic soaps and body washes.
   a. true
   b. false

10. The first step in an effective action plan for the management of AD is:
    a. good basic skin care and the avoidance of irritants and allergens.
    b. treatment with high-potency corticosteroids.
    c. treatment with topical CNIs.
    d. none of the above

Statement of Participation Evaluation

IMPORTANT: Please print all information below. Posttests without complete name and mailing address cannot be processed for CME credit.
A statement of credit will be mailed in 6 to 8 weeks.

Name: ____________________________ Date: _______________________
Degree (circle): MD, DO, other (specify): __________________________
Specialty: ____________________________________________________
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I participated in this educational activity for the following length of time:
☐ 30 min  ☐ 1 hr  ☐ 1 hr 30 min  ☐ 2 hr

ACTIVITY EVALUATION

1. After completing this activity, I am able to:
   a. identify the skin lesions that are characteristic of AD and differentiate them from other common skin disorders.
   b. describe the role of allergens and irritants in AD and help patients/parents understand how to avoid them.
   c. list the two main classes of topical therapies available for patients with AD and summarize their benefits and risks.
   d. outline and communicate specific strategies for the long-term management of individual patients with AD.
   e. prevention of subsequent flare reactions in patients of all ages.
   f. reduce the time to first flare.
   g. an increase in the time to first flare and time between subsequent flares.
   h. all of the above

2. The information was relevant to my practice.
   a. true
   b. false

3. The activity provided new information.
   a. true
   b. false

4. The information was communicated clearly.
   a. true
   b. false

5. The overall quality of the educational content was satisfactory.
   a. true
   b. false

6. The format of this activity was conducive to learning.
   a. true
   b. false

7. Did you perceive inappropriate commercial influence for or against a specific commercial product in the program content?
   a. true
   b. false

8. Additional comments:
   __________________________

Suggested topics for future activities:
____________________________

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