A Supplement to
Pediatric News®

Current Issues in the
Management of
Atopic Dermatitis in
the Pediatric Patient

Highlights of a Clinical Roundtable

Atopic Dermatitis Today:
A Brief Overview

Topical Calcineurin Inhibitors:
A Critical Analysis of Current
Issues

Skin Cancer and
Immunosuppression

Lymphomas:
Clarifying the Issues

Significance of Calcineurin
Inhibitors

Treatment of Atopic Dermatitis
in Infants

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The study of topical corticosteroids is complicated by the fact that these agents can be highly effective in the treatment of atopic dermatitis, but they also have the potential for serious adverse effects when used long-term. Atopic dermatitis is a chronic inflammatory skin disease that is extremely common in childhood. The prevalence of this condition has been increasing in recent decades and is now estimated to affect more than 17% of children in the United States. Atropic dermatitis frequently precludes development of asthma and allergic rhinitis in later childhood.

Because traditional treatment regimens for atopic dermatitis center on topical corticosteroids, physicians need to understand the role of topical calcineurin inhibitors in treatment. The two corticosteroid-free topical medications, pimecrolimus and tacrolimus, add to the clinician’s options for managing this complex and poorly understood disease.

Atropic dermatitis is characterized by itching, flaking, and inflamed skin, and these signs and symptoms often are accompanied by considerable discomfort and social embarrassment. Moreover, atropic dermatitis is associated with the risk for complications, including serious skin infections. This knowledge is particularly important in the light of the US Food and Drug Administration’s (FDA) recent advisory letter to clinicians regarding the topical calcineurin inhibitors. For these reasons, clinicians need to remain up-to-date on the benefits and risks of all of the available treatments for atropic dermatitis and understand the proper use of these therapies.

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

- Understand and list the risks and benefits, efficacy, and safety of topical corticosteroids and topical calcineurin inhibitors to treat atropic dermatitis.
- Recognize the clinical distinctions between atropic dermatitis and early stage cutaneous T-cell lymphoma.
- Explain how calcineurin inhibitors fit into the long-term management of atropic dermatitis and the role of other treatments, including topical corticosteroids, further discussion of steroids which cannot be used long term.
- Discuss the major issues in the controversy over the purported risk for cancer resulting from the use of topical calcineurin inhibitors.
- Explain the difference between health risks associated with topical calcineurin inhibitors versus those associated with oral formulations of these agents.
Introduction

As most dermatologists and pediatricians are aware, the Pediatric Advisory Subcommittee of the US Food and Drug Administration (FDA) met on February 15, 2005 to discuss calcineurin inhibitors (Table, on page 7). As a result of that meeting, the FDA issued public health advisories regarding pimecrolimus and tacrolimus, which cautioned health care professionals and consumers about a potential cancer risk from the use of these drugs. The Advisory Subcommittee proposed changes in the labeling for the topical calcineurin inhibitors, including, specifically, the addition of a black box warning regarding the possible risk for cancer as well as a patient advisory brochure that would discuss the potential risk for cancer.

As a result, many dermatologists and pediatricians either have stopped prescribing topical calcineurin inhibitors or have changed their prescribing patterns. Some are concerned about the putative increased risk for lymphoma or skin cancer; many are wary of the risk for legal liability and have spent significant time counseling parents and convincing some insurance companies that treatment with topical calcineurin inhibitors is appropriate and safe.

The incidence of atopic dermatitis in the United States is significant and is on the rise, currently estimated to range between 7% and 21% of the general population. In about 60% of cases, the disease first appears within the first year of life, with another 25% developing between 1 and 5 years of age.1-3

The disease is recognized as a genetic disorder, probably with an autosomal dominant inheritance. The likelihood of a child developing atopic dermatitis, asthma, and/or allergic rhinitis is about 60% if one parent has an atopic diathesis and 80% if both parents are affected.4

In most patients, the appearance of skin symptoms early in life marks the beginning of what has become known as the “atopic march.” Atopic dermatitis is seen in infancy or early childhood, followed closely by food allergies, and asthma appearing by about 2½ years of age in many children (with the incidence peaking at 5 or 6 years of age). Allergic rhinitis is the final manifestation.5

It has been suggested that interruption of the early expression of atopic dermatitis may lead to a decrease in the incidence of asthma and allergic rhinitis.5 A large multicenter study is currently under way to test the potential benefits of early intervention in patients with atopic dermatitis.

Severity and Complications

The severity of atopic dermatitis at onset ranges from mild to severe. The tendency over time is for the disease to become less severe, although 60% of children with atopic dermatitis will have some manifestation of the disease throughout adolescence and adulthood.6,7

In addition to the discomfort patients experience (pruritus, scaling, crusting, oozing, and pain), atopic dermatitis is associated with skin infections, in some cases progressing to systemic sepsis. About 90% of patients with this disease carry Staphylococcus aureus as part of their normal skin flora, and it seems that individuals with atopic dermatitis have an immune defect that increases the risk for both S. aureus and certain viral skin infections, particularly...
**Herpes simplex**, which may become extensive and severe.

**Multifaceted Approach to Therapy**

Monotherapy is not an effective strategy for atopic dermatitis and, in addition to neither improving nor inhibiting symptoms, is likely to result in persistence of patient discomfort and dissatisfaction. Combination therapy, utilizing basic cleansing and moisturizing measures as well as appropriate pharmacologic treatment, provides the greatest chance for clinical success, both short and long term.

The mainstays of basic treatment and maintenance have been good bathing techniques and the application of emollients to wet skin. These remain the foundation of any treatment or maintenance regimen, and their importance cannot be stressed too strongly to patients and their parents.

Regarding medications, topical corticosteroids have been effective agents for many years and, used judiciously, still play an important role in the treatment of atopic dermatitis. Ultraviolet light therapy is still a valuable and effective mode of treatment of the disease in atopic patients refractory to other modalities.

When cutaneous *S. aureus* overgrowth occurs, topical and/or systemic antibiotic therapy is appropriate. Similarly, because herpes simplex infections (eczema herpeticum) may spread rapidly, the early use of systemic antiviral agents in this patient group is important.

Because mast-cell histamine plays a minor role in the pathogenesis of atopic dermatitis, treatment with antihistamines may be considered. However, there are no double-blind, placebo-controlled studies demonstrating the efficacy of this class of drugs in patients with atopic dermatitis. Nevertheless, antihistamines may be helpful for their soporific properties, allowing patients to have a more restful sleep. A small percentage of children and adults require treatment with systemic immunosuppressants to control their disease.

The introduction of the topical calcineurin inhibitors has greatly improved the clinical picture for patients with atopic dermatitis. The ready acceptance of topical calcineurin inhibitors over the last few years by physicians and, increasingly, by patients, shows that this class of drugs has filled a critical space in the roster of available treatments. These drugs have been shown to be highly effective, but clinicians should keep in mind that basic management measures must accompany any pharmacologic treatment regimen.

**Patient/Parent Satisfaction**

A study based on telephone interviews conducted by the National Eczema Association for Science and Education several years ago—prior to the introduction of topical calcineurin inhibitors—indicated that patients or their parents had a somewhat high level of satisfaction with their physicians. When asked about their level of satisfaction with the therapeutic modalities, the respondents said they were highly unsatisfied and frustrated by the measures available at that time to treat atopic dermatitis. This study demonstrated that clinicians, in general, were perceived as doing their best to manage the clinical challenges that these patients presented. It also showed clearly that a new approach to therapy was needed.

**Conclusion**

Increasingly, dermatologists and pediatricians are educating parents and patients about the importance of early intervention in preventing a severe flare-up of symptoms. All patients should always employ good bathing techniques and apply emollients liberally to wet skin as part of their regular daily skin care. When a few papules or even pruritus alone occurs, the prompt application of a topical calcineurin inhibitor to the involved site can be highly effective in controlling the disease, often without the need for concomitant topical corticosteroid therapy.

Adequate patient/parent counseling about the disease and the importance of good skin care is crucial to treatment success, and effective counseling sessions take time. Furthermore, such educational sessions should be repeated occasionally to reinforce important messages and to provide time for patients and/or parents to ask questions and express concerns. Time invested this way fosters understanding about the disease and how it is managed, and is likely to lead to a better therapeutic outcome and less frequent office visits for intervention due to a flare-up of the disease.

**References**


Topical Calcineurin Inhibitors: A Critical Analysis of Current Issues

DR LEYDEN: Let’s begin with some history behind the recent US Food and Drug Administration (FDA) decision.

DR ORLOW: In October 2003, a Pediatric Safety Subcommittee of the Infectious Disease Advisory Committee of the FDA was convened for the purpose of discussing long-term therapies for atopic dermatitis, including the question of a registry for patients on topical calcineurin inhibitors. However, the discussion veered toward the issue of a possible risk for lymphoma, and a suggestion was made to include a black box warning to that effect in the labeling. It’s important to remember that an FDA Advisory Committee is just that: it reviews issues and makes recommendations but has no power to mandate any FDA actions, including changes in labeling (see “FDA Advisory Committees: An Overview” on page 8). At that time, the FDA’s Division of Dermatologic and Dental Drugs reviewed that recommendation and determined that such a warning was not warranted.

In February 2005, the Pediatric Safety Committee was again convened by the FDA and asked to reconsider the safety of the topical calcineurin inhibitors. Presentations were made by representatives of the FDA’s Office of Drug Safety (Table on page 7) and others to the Advisory Committee. These presentations indicated that the calcineurin inhibitors are being used in a large number of children and the medications are relatively new, so the potential for and extent of long-term side effects—say, 10 years from now—are unknown. I think it’s fair to say that the members of the Advisory Committee then spent a substantial amount of time discussing prescribers’ patterns and use of these medications in children under 2 years of age.

Skin Cancer and Immunosuppression

DR LEYDEN: That meeting began with a very detailed presentation about the kinds of problems that have been seen in immunosuppressed patients. Increasing numbers of solid-organ transplant recipients are surviving longer, and these individuals commonly develop multiple nonmelanoma skin cancers within 5 or 6 years after their surgery. Clearly, an intact immune system is involved in preventing nonmelanoma skin cancer. We have also seen that psoralen plus ultraviolet A (PUVA), an effective treatment for psoriasis, can be associated with the development of skin cancer. Might long-term use of calcineurin inhibitors be involved in promoting squamous cell cancer? This is a different but legitimate question. The companies that make pimecrolimus and tacrolimus have committed to phase IV studies—now under way—to address this issue. Ten-year registries have been established that will be linked with cancer registries, which I believe is a good way to proceed with answering the concerns about cancer. Also, case-control studies are being set up to determine whether a risk for melanoma and nonmelanoma skin cancers exist in patients having received topical calcineurin inhibitors.

Further, an additional study is being established in patients who are positive for human immunodeficiency virus.

DR ORLOW: And the reason the FDA was concerned about these issues is that patients on oral calcineurin inhibitors and other immunosuppressive agents can develop squamous cell carcinoma. However, patients who have had squamous cell carcinomas in the setting of renal transplantation usually have molecular evidence of human papillomavirus infection, and, of course, they also are exposed to uninterrupted use of an oral immunosuppressant. Unlike the overwhelming majority of our patients with atopic dermatitis using these agents topically, transplant patients are not told, “At the first signs or symptoms of rejection, please take your capsules to abort rejection of your transplant.” Of course, there is a subset of patients with truly severe atopic dermatitis who are on topical tacrolimus or pimecrolimus continuously.

DR LEYDEN: That’s an interesting population, and a case control study is under way to look at that risk. You could also ask the same thing about corticosteroids. We know that corticosteroids cause apoptosis in Langerhans’ cells and depletion of these cells. The calcineurin inhibitors do not have that effect, so you could argue that, from the immune surveillance point of view, these agents probably are safer.

DR ORLOW: When it comes to cutaneous squamous cell carcinoma, you might imagine, theoretically, that immunosuppressed patients exposed to ultraviolet (UV) light could manifest a cancer after they are off the drug. This is different from the situation with lymphoma, where it is difficult to come up with any cogent argument explaining how a lymphoma would occur long after cessation of calcineurin inhibitor treatment.

In the case of topical tacrolimus, there was some suggestion of an associated cancer risk from studies in hairless mice.
in which UV radiation was used to accelerate the time to appearance of the first skin cancer. In the studies of topical pimecrolimus in hairless mice, no difference was seen between the mice in the pimecrolimus group and those in the vehicle-only group. If either agent was blocking DNA repair in vivo, one would certainly expect to see a robust signal in that model.

DR LEYDEN: That’s important. In the preclinical safety data, there was no evidence that topical applications of pimecrolimus resulted in any acceleration or changes in UV carcinogenesis.

Lymphomas: Clarifying the Issues

DR ORLOW: At the previous Advisory Committee meeting in 2003, one of the members made a statement about the “known lethal consequences” of topical pimecrolimus and tacrolimus. In addition, the results of studies of oral calcineurin inhibitors in monkeys were mentioned at the 2005 meeting. However, primate studies of the oral forms of these drugs were not done as part of the development of the topical forms; they do not have to be. Many people don’t realize that.

DR LEYDEN: That’s very important for clinicians to understand. For example, a 39-week, preclinical toxicity study was conducted using oral pimecrolimus in monkeys. The researchers observed a dose-related, immunosuppression-related, lymphoproliferative disorder (IRLD) that was associated with opportunistic infections. These effects were seen beginning at a dosage of 15 mg/kg/day, which is equivalent to 31 times the maximum individual exposure seen in the clinical trials involving topical pimecrolimus in pediatric patients. When administration of the drug was stopped, the researchers reported that the monkeys recovered and/or that these effects were at least partially reversible. The results of those studies caused undue concern at the recent Advisory Subcommittee meeting.

DR ORLOW: Yes, but I think that the human oral exposure data are helpful from the standpoint of safety. The question in the phase II studies of oral pimecrolimus was whether it was less nephrotoxic than cyclosporine. But important from the standpoint of the safety of topical use was that the human trials also showed that 3 months of continuous oral pimecrolimus use did not result in the development of any lymphomas. And remember that these study subjects had much higher sustained blood levels than any patient might occasionally get using topical calcineurin inhibitors.

DR LEYDEN: Much discussion and detail at the February 2005 Advisory Committee meeting centered on post-organ-transplant lymphoma, the “benign” hyperlymphoproliferation that occurs in the posttransplant setting. These are primarily B-cell lymphomas with a particular phenotype: they frequently are extranodal, Epstein-Barr virus (EBV) can be demonstrated in the tumor cells (with loss of B-cell antigens), and they can regress on discontinuation, a decrease in, or modification of the immunosuppressive regimen. Therefore, this clearly is a specific type of systemic lymphoma that occurs in the posttransplant setting and has not been seen in patients using topical calcineurin inhibitors.

The reported cases of lymphomas in all patients who have used topical calcineurin inhibitors have clinical features and phenotypes that are different from what is seen in the immunocompromised population.

DR GUINAN: The presentation about lymphomas did not emphasize those differences. The immune suppression associated with oral or topical calcineurin inhibitors alone is not the same as what is seen with organ transplant recipients; the latter tend to develop non-Hodgkin’s lymphomas in the context of long-term, multiagent immunosuppression and also are predisposed to a variety of other solid tumors.

DR LEYDEN: IRLD and lymphoma were seen in studies in monkeys, but only with high oral dosing—at least 31 times the maximal recorded human dose (RHD). The data that the FDA reviewed at that time also showed that topical calcineurin inhibitors are nonmutagenic, nongenotoxic, and nonteratogenic. The incidence of photocarcinogenicity was not statistically different from that seen with vehicle alone, in the case of pimecrolimus. In a 1-year photocarcinogenicity study using topical tacrolimus in hairless mice, the investigators found that the median time to the onset of the formation of tumors decreased after applications of the ointment.7

DR ORLOW: There are published data in which adult patients with psoriasis or atopic dermatitis took oral pimecrolimus for 3 months, and none developed lymphoma. Although these data must be confirmed in longer-term studies, I find it difficult to believe that even if a patient using the topical form of the medication had some systemic absorption occasionally, that this would result in lymphoma.

First, the notion of systemic absorption of the topical calcineurin inhibitors is not supported by most of the data. Second,
how would a patient develop lymphoma from topical application when it has been demonstrated that ongoing, continuous immunosuppression would be required for this to occur? Third, patients who took pimecrolimus orally for 3 months didn’t develop the disease.

**DR GUINAN:** Many patients have used high doses of potent systemic calcineurin inhibitors for long periods of time, and most of them have not developed lymphomas. For example, there is only one case report of a patient who developed lymphoma after long-term use of cyclosporine for aplastic anemia.9 This is one case among the thousands of patients with this disease, and these are patients who typically receive cyclosporine at high oral doses for about 18 months and achieve daily trough levels of the drug of 200 ng/mL. It is not known whether that case was drug related.

**DR LEYDEN:** What does the transplant literature say about the time from the beginning of oral calcineurin inhibitor use to the development of IRLD?

**DR GUINAN:** Patients who have received organ transplants have a substantial antigenic challenge, and more than one drug, not just an oral calcineurin inhibitor, is always used in their immunosuppressive regimen. In these patients, IRLD comes in two waves. In the first year, the classic presentation is a virulent EBV-related, early B-cell lymphoma characterized by histology that evolves from a pleomorphic to a monomorphic picture. A second wave of IRLD—which still contains a high proportion of B-cell non-Hodgkin’s lymphoma but now also contains T-cell non-Hodgkin’s lymphoma—has been observed in cardiac transplant and other solid-organ transplant recipients at 5 to 6 years after surgery, or even later. In this latter group, the histologies are more bizarre and less conserved, and the outcomes are even worse. These are patients who have been on multiagent immunosuppression for very long periods, with the antigenic challenge of a donor organ always present.

**DR ORLOW:** I think there are two other issues that add to the confusion. In speaking to other clinicians, I find that many tend to consider all lymphomas as a single disease. For example, clinicians generally understand that to say, simply, “skin cancer” does not tell the whole story—there are basal cell carcinomas, squamous cell carcinomas, malignant melanomas, and so forth, and even though basal cell and squamous cell carcinomas arise from the same cell type, they behave entirely differently. With lymphomas it’s so important for clinicians to realize that there are multiple kinds and that very specific types of lymphomas are associated with immunosuppression. The second problem is that the development of lymphoma related to oral calcineurin inhibitors is a process that happens while you are on the drug and requires continuous, sustained exposure for an extended period of time—it’s not something that happens years later.

**DR GUINAN:** Correct. In fact, the treatment of choice for early, classic IRLD is to decrease the intensity of immunosuppression. A priori, therefore, it does not make sense that a drug used intermittently—such as a topical immunosuppressant—will cause lymphoma. Given that decreased intensity, and not always cessation, of immunosuppression can result in resolution of disease, achieving intermittent blood levels of topically administered calcineurin inhibitors during treatment is likely to be helpful. This is the kind of information that clinicians should be aware of to increase their own comfort level and to allow them to explain the facts to their patients.

A related issue is that IRLD is a specific syndrome characterized by particular histology and clinical presentation. It is illogical that if a topical calcineurin inhibitor is causing IRLD, there is not a single reported case of a
rapidly proliferative polyclonal tumor, proceeding to a monoclonal, EBV-related, fast-moving tumor. Patients with IRLD often have a very rapid course of decline, and it’s hard to miss the diagnosis. Patients can die in a matter of days after a diagnosis.

**Cutaneous T-Cell Lymphoma versus Atopic Dermatitis**

**DR GUINAN:** It appears to me that some clinicians are confusing cutaneous T-cell lymphomas (CTCL) with atopic dermatitis. What happens in such cases is that patients with CTCL are misdiagnosed as having atopic dermatitis, and when they develop clinical signs of lymphoma, the conclusion is that the treatment caused lymphoma. Misdiagnosis is the actual culprit, not the treatment.

**DR LESSIN:** In the review of the data presented to the FDA, it was apparent—as has already been stated here—that no lymphomas seen in patients on calcineurin inhibitors were related to immunosuppression. I think the biggest concern among dermatologists and pediatricians—and particularly among dermatologists, who are in a position to diagnose CTCL (or mycosis fungoides) more often than are clinicians in the other specialties—is whether the use of topical calcineurin inhibitors increases the risk for CTCL. The answer is it does not, and that is based on the data that were presented both before and after these drugs were approved.

The critical clinical point is that many times in this context, as Dr Guinan just stated, CTCL presents as a dermatitis that is essentially misdiagnosed, when it is really CTCL from the outset and not atopic dermatitis transforming to CTCL—with or without the use of a topical corticosteroid or a topical calcineurin inhibitor. That information should alleviate part of the fear factor that has emerged and escalated recently.

In the data that were available at the 2005 Advisory Panel presentation, there were some peripheral T-cell lymphomas, but again, looking down that list of lymphomas, they were not related to the typical immunosuppressive lymphoproliferative diseases.

**DR ORLOW:** Does immunosuppression even have a role in the pathogenesis of CTCL? Are there any data from animal or human studies showing this?

**DR LESSIN:** Essentially, no. The etiology of CTCL is still unknown. Cases have been reported showing the exacerbation of CTCL with the use of oral calcineurin inhibitors, so the oral form of these drugs should not be used in patients with CTCL. However, what clinicians are now concerned about, in this climate of fear, is whether the use of a topical calcineurin inhibitor in a patient with atopic dermatitis will cause mycosis fungoides. There is no evidence for this.

**DR LEYDEN:** T-cell lymphomas are far less common than B-cell lymphomas. The T-cell lymphomas usually appear after many years of sustained, multiagent immunosuppression. Further, the T-cell lymphomas—that is, CTCLs—that have been described in that setting are not the type that most nondermatologists ever see in practice.

How many and what types of lymphomas have been reported to date in patients on topical calcineurin inhibitors?

**DR ORLOW:** For tacrolimus, during the first 3 years it was on the US market, 11 lymphomas had been reported as of December 31, 2004. Of these, five were noncutaneous and six were CTCL. None were in children. At that point, 1.7 million people had been treated with topical tacrolimus.

In the case of pimecrolimus, as reported to the Pediatric Advisory Committee at the 2005 meeting, more than 5 million patients have been treated with the topical form of this drug, more than half of them children. As of December 31, 2004, four cases of lymphoma (including one case of non-Hodgkin’s lymphoma in a 2-year-old child) and two cases of cutaneous malignancy (one squamous cell and one basal cell carcinoma) have been reached.

**Infections and Topical Calcineurin Inhibitors:**

**The Data in Perspective**

**DR ORLOW:** What about skin infection? Just to play devil’s advocate for a moment, in the controlled, 12-week studies for tacrolimus, an increased incidence was seen in certain infections, such as eczema herpeticum and folliculitis on the legs. This was a small number, representing 2% of the patients in the study who received tacrolimus, compared to 0.8% of those who received vehicle only, and, in long-term studies (3 years and beyond), no increase in the incidence of any cutaneous infection was seen over time. But do we believe that there is the possibility of increased cutaneous infections from the use of topical calcineurin inhibitors?

**DR EICHENFIELD:** In both the tacrolimus and the pimecrolimus studies, there were signals that suggested there might be an increased risk of infections related to herpesviruses, which—depending on which studies you look at—are called varicella or herpes infections. Clearly, the labeling of these two drugs accounts for that potential risk, and clinicians are advised not to use these medications in the presence of active skin infections. In clinical practice—for most cutaneous infections, including impetiginized atopic dermatitis—there is not an increased risk of cutaneous infection with these medicines when used in appropriate regimens. In fact, there may be a decreased prevalence of cutaneous infection if there is better control of the inflammatory disease of the skin.

**DR ORLOW:** There are certainly studies...
for topical corticosteroids, and I have seen abstracts for calcineurin inhibitors showing a decrease in *Staphylococcus* carriage in active lesions of eczema upon treatment. This makes sense, because if the eczematous area is removed, the nidus for colonization no longer exists.

**DR LEYDEN:** Interestingly, not everyone initially accepted that story, based on the logic that if eczema was colonized so heavily and so frequently, the application of a topical corticosteroid would cause abscesses, cellulitis, or worse. But, as Dr Orlow points out, as the inflammatory environment is decreased, the flora takes care of itself through other mechanisms. That has been seen with the calcineurin inhibitors as well.

I do agree with Dr Eichenfield that if there is an issue with infection, it concerns herpes simplex. I don’t think significant, widespread herpes infections have been seen, but there may be a slight increase in minor herpes simplex infections.

**DR ORLOW:** Dr Eichenfield alluded to the infant data and systemic infections. The Advisory Committee had concerns about an increased incidence of pharyngitis, influenza, coughs, and coryza in infants on topical pimecrolimus, for example. Do you want to elaborate on those studies?

**DR EICHENFIELD:** Right now, the topical calcineurin inhibitors carry labels indicating that systemic infections may be increased, as seen in the core studies and the initial drug filings with the FDA. Therefore, this is not new information—the data were listed on filing for both drugs. The standard procedure is that if an increased incidence of a particular event is seen during a clinical study, the labeling may include wording stating this. Usually, vehicle- or placebo-controlled studies can determine whether, in fact, the event is even attributable to the drug.

If you analyze the data from those original studies with a correction for time in the study, you get very different conclusions about the infection rate with use of calcineurin inhibitors. Remember, in a vehicle-controlled study, the patients or their families don’t know whether they are in the active-treatment or vehicle-only group, so if the patient’s eczema is not improving, he or she may choose to leave the study. This is especially true in pediatric studies, in which it is unethical to keep patients in the study if the disease is worsening and other medications are available to effectively treat it.

In any study, patients randomized to receive active medicine tend to finish the study course, whereas more patients in the vehicle group quit the study early. In collecting data on infections and other adverse effects, the more time patients are in the study, the more likely that intercurrent events and infections occur, even if they are not attributable to the study medication.

Therefore, in evaluating the data on pimecrolimus, for example, and correcting for the time in the study, if one looks for signals of an increase or decrease in systemic infections in the two groups—that is, active treatment and vehicle only—there are no significant increases in systemic infections. These findings are reflected in the fairly extensive clinical experience with both of the topical calcineurin inhibitors to date.

Another concern that was raised at the FDA presentation is sporadic high levels of topical calcineurin inhibitors that had been measured in children. One patient receiving topical tacrolimus was admitted to the hospital with *Pseudomonas* sepsis.

I have two comments about this. First, it is very hard to know if the patients discussed in that presentation had atopic dermatitis. Most of them appeared to have either Netherton’s or graft-versus-host disease. The use of topical tacrolimus in patients with Netherton’s is a known problem. The use of this drug in patients with graft-versus-host disease is not yet a reported risk factor for systemic levels with topical use of tacrolimus, but I assume that it soon will be.

I don’t know if anyone who had access to those data, other than the FDA, was able to assess whether any of the patients with high blood levels had “garden variety” atopic dermatitis. Does anyone else have any comments on this?

**DR LEYDEN:** I think the point of view would be that if the blood levels are a problem, that issue should be addressed. **DR ORLOW:** The patient in question—with *Pseudomonas* sepsis—purportedly had a high level a week after stopping tacrolimus.

**DR GUINAN:** Yes, the blood level reportedly seen in that patient made no sense relative to the drug’s half-life. The factors that could explain such a finding were not presented. For example, did the patient have kidney dysfunction or an intrinsic liver problem? More to the point, was this a patient who was on other drugs that could interfere with tacrolimus metabolism?

**DR LEYDEN:** I agree, but think of it from the FDA’s point of view. Let’s say that there is a situation in which a patient does not have atopic dermatitis and has poor renal function. It is reasonable to assume that, in such a case, the patient has a skin disorder that will not respond to a calcineurin inhibitor, yet the topical agent is being applied frequently and in large amounts. Let’s further assume that a certain blood level is reached, and—although it is not likely—the clinician is not aware of the clinical entity of Netherton’s disease or is not familiar with the principle that some drugs accumulate in a patient with poor renal function. This presents a potential risk if that blood level was immunosuppressive, which, in the case of the reported patient, it clearly was.

**DR GUINAN:** I can certainly imagine a
child with severe atopic dermatitis who may have increased absorption of a topical calcineurin inhibitor and who also has, for example, mucosal Candida. Imagine that, in this scenario, a prescription is written for an oral medication such as fluconazole or, worse from the point of view of drug clearance, itraconazole. At that point, the calcineurin inhibitor is not metabolized and cleared, and the blood level of the drug doubles within 24 hours. It’s important for clinicians to be aware of the potential for drug-drug interactions.

**Significance of Calcineurin Inhibitor Blood Levels**

**DR ORLOW:** In adults and children using topical tacrolimus 0.1%—a concentration higher than what is FDA approved for pediatric use—60% had blood levels below 0.5 ng/mL, 15% to 20% had blood levels between 0.5 and less than 1 ng/mL, and a few had levels of 1 to 5 ng/mL. No patients had blood levels above 5 ng/mL.13

In studies involving children using topical pimecrolimus 1%, 87% of patients had blood levels less than 0.5 ng/mL, 12% between 0.5 and less than 1 ng/mL, and 1% between 1 and 2 ng/mL, with no patients having blood levels higher than 2.6 ng/mL.10 The point is that low blood levels of these agents, no matter how long the treatment period, will just not result in immunosuppression.14

**DR LEYDEN:** That is correct, and the original Advisory Committee that reviewed tacrolimus for its FDA approval in 2000 considered these data. However, those who were on the committee in February 2005 focused on the results of animal studies, which showed much higher blood levels in rodents exposed to topical calcineurin inhibitors. It’s important to understand that blood levels that are achievable from topical exposure in rodents are very different from those achievable in humans. The area-under-the-curve comparison between patients with atopic dermatitis, patients with posttransplant IRLD, and mice exposed to the topical form of the medication showed that mice get systemic exposure from cutaneous application that is comparable to what transplant patients get from systemic dosing. In contrast, cutaneous application in humans yields an order of magnitude less.

**DR ORLOW:** Also, unfortunately, the initialism “RHD” was interpreted as maximal recommended human dose rather than maximal recorded human dose. The result is that some clinicians believe that the RHD is the blood level that patients typically achieve. Instead, the RHDs are worst-case-scenario levels observed in patients in pharmacokinetic studies, calculated as if these levels persisted for 24 hours a day continuously during the use of the drug.

**DR GUINAN:** In solid-organ transplant recipients, a very low-end therapeutic level of tacrolimus is 3 ng/mL. Most patients are managed in the range of 5 to 8 ng/mL, and many require between 5 and 12 ng/mL or even higher. So the levels seen in the topical tacrolimus studies are extremely low.

**DR LEYDEN:** The FDA approved these drugs in the first place because the members of the original Advisory Committee determined that the systemic exposure was insignificant and that there was not enough absorption to represent a risk of immunosuppression.

**Childhood Vaccine Responses**

**DR LEYDEN:** It might also be worth mentioning that studies have been published showing that the topical calcineurin inhibitors, even when used chronically, have had no effect on anti-body response to rubella, measles, diphtheria, tetanus, or pneumococcal vaccinations.13,16 In a study involving 112 children, use of topical calcineurin inhibitors for 1 year showed no effect on skin tests for T-cell response, tuberculosis, diphtheria, or Candida.10 The study of tacrolimus by Stiehm and colleagues showed that 7-week, twice-daily applications of topical tacrolimus 0.03% had no effect on the patients’ serologic response to a 23-valent pneumococcal polysaccharide vaccine.16 If these agents are having some subtle immunosuppressive effects, one would expect to see different results.

**DR EICHENFIELD:** I would stress this point for the pediatricians in our reading audience. Those of us who have used topical calcineurin inhibitors extensively in children—including the use of these drugs off-label in children under 2 years of age—have been closely monitoring our patients and carefully following the studies for evidence of subtle immune effects from the use of these drugs. In fact, the studies using standard antigen testing for vaccine response rates and T-cell responses have been reassuring: there is no impact.16,17 The published study with tacrolimus demonstrated that there certainly is no systemic immunosuppression, and there are no subtle changes in immune response with topical use of this drug. This included immunoglobulin levels and complete blood counts.

A study currently is under way to determine the effects of topical pimecrolimus on immunoglobulin and complete blood counts following routine childhood vaccinations.10

**Combination Topical Therapy**

**DR LESSIN:** Another issue that may be worth addressing is the experience of using topical calcineurin inhibitors and topical corticosteroids. Would combined use cause problems? As far as I’m concerned, the answer would be that it does not, but are there any data on this combination?

**DR ORLOW:** There are no long-term safety data. The only data we have so far are, by and large, negative data showing there is little or no benefit to combination therapy using an agent from each class. We know that topical calcineurin...
A. MILD DERMATITIS (Defined by disease extent or persistence)

<table>
<thead>
<tr>
<th>Step</th>
<th>Step 2</th>
<th>Step 3</th>
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<tr>
<td>Emollient bid</td>
<td>Emollient bid</td>
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<tr>
<td>Intermittent low potency TS for flare control</td>
<td>Mid-potency TS for flare control</td>
<td>TCI alternative</td>
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<tr>
<td>+/- Antihistamines</td>
<td>+/- Antihistamines</td>
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Step forward if necessary, back to step 1 if controlled. Maintenance therapy beyond Step 1 if disease recurs frequently or persists.

B. MODERATE DERMATITIS (Defined by disease extent or persistence)

<table>
<thead>
<tr>
<th>Step</th>
<th>Step 2</th>
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<td>Emollient bid</td>
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<tr>
<td>Intermittent low potency TS for flare control</td>
<td>Mid-potency TS for flare control</td>
<td>Higher potency TS for flare control</td>
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<tr>
<td>TCI alternative</td>
<td>TCI long-term intermittent</td>
<td>TCI alternative</td>
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<td>+/- Antihistamines</td>
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<tr>
<td>Antibiotic if clinical infection</td>
<td>Antibiotic if clinical infection</td>
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Step forward if necessary, back one step if controlled. Maintenance therapy as in Step 2 if disease recurs frequently or persists. Consider Step 5 if uncontrolled: phototherapy, other systemic therapy.

C. SEVERE DERMATITIS (Defined by disease extent or persistence)

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<tr>
<th>Step</th>
<th>Step 2</th>
<th>Step 3</th>
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<td>Emollient bid</td>
<td>Emollient bid</td>
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<td>Phototherapy or Systemic therapy</td>
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<tr>
<td>Mid to higher potency TS for flare control (may be used instead of or in addition to TCI)</td>
<td>Higher potency TS for flare control</td>
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<td>+/- Antihistamines</td>
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<td>Antibiotic if clinical infection</td>
<td>Antibiotic if clinical infection</td>
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Step forward if necessary, back one step if controlled. Standard maintenance therapy; Step 4 if uncontrolled; Step 5 as needed.

*Good skin care and avoidance of irritants and allergens are part of base therapy preceding Step 1.
†Changes in steps are in bold type.
TCI=topical calcineurin inhibitor; TS=topical corticosteroids


Inhibitors block T-cell activation, as do topical corticosteroids. However, topical corticosteroids can have other effects on many other cell types in the skin—including Langerhans’ cells, endothelial cells, and fibroblasts—that calcineurin inhibitors don’t.

DR LEYDEN: One of the issues that came up was maintenance therapy. Should calcineurin inhibitors be used as part of maintenance therapy?

DR LESSIN: Many dermatologists look for corticosteroid-sparing agents and consider calcineurin inhibitors to be corticosteroid-sparing agents. They may use a protocol similar to what is often used in patients with psoriasis: calcineurin inhibitors on weekdays and steroids on the weekend. I use an algorithm of care for atopic dermatitis based on the model that was published by Larry Eichenfield (see “Proposed Algorithm for Severity-Based Step Therapy of Atopic Dermatitis,” at left).18

DR EICHENFIELD: Atopic dermatitis is a disease that can be persistent or intermittent, often with tremendous variability. The course depends on some intrinsic factors related to the severity of an individual’s disease as well as to external factors that may exacerbate the dermatitis. Some factors may be specific and others may not be identified. Therefore, great variation exists in how active the disease is from a temporal standpoint.

Maintenance therapy has always been part of the treatment of atopic dermatitis, with a very strong emphasis on nonpharmacologic maintenance. Good skin care and liberal use of moisturizers are the basis of therapy. Unfortunately, this maintenance regimen is sufficient for only a small subset of patients. Depending on disease severity, a clinician must be ready to utilize a mixture of medications to maintain good disease control.

Some clinicians substitute calcineurin inhibitors as first-line maintenance therapy, neglecting to implement the standard base therapy of good skin care and frequent moisturization. In my opinion, this is an inappropriate use of the calcineurin inhibitors.

On the other hand, there are many patients who have persistent disease...
who promptly flare when their medication is stopped or who have frequently recurring disease. These are the patients in whom a maintenance regimen consisting only of nonprescription emollients and topical corticosteroids is very restrictive. In this population, the calcineurin inhibitors represent a breakthrough in our ability to maintain a relatively disease-free state.

My use of pimecrolimus and tacrolimus in cases of persistent or frequently recurring atopic dermatitis has not been changed by the discussion of potential black box concerns. Disease severity drives the need for these particular agents, and most experts believe that intermittent, long-term use is quite safe. In fact, such use of calcineurin inhibitors is possibly much safer than the alternative: persistent, continuous use of higher-potency topical corticosteroids.

**DR ORLOW:** What about the published studies that address using intermittent topical corticosteroids as maintenance therapy?

**DR EICHENFIELD:** Certainly there have been some studies that have looked at intermittent use of those agents. Probably the best study involved topical fluticasone, in which patients were given that drug to use on a regular QD to BID schedule. After several weeks, only the patients did well with a twice-weekly. A substantial percentage of patients did not make it into the long-term study because their disease was not controlled with fluticasone. A subset of those patients did well with a twice-weekly fluticasone maintenance regimen, but it is clear from this study that fluticasone is not sufficient in a good number of patients: 163 of 295 patients had a relapse or discontinued the study within the 16-week period.

**DR GUINAN:** Do you think that the concerns generated recently about topical calcineurin inhibitors will drive clinicians to use more topical corticosteroids instead?

**DR ORLOW:** The argument may be that calcineurin inhibitors are the most intensively studied topical agents in the history of formal clinical trials in dermatology. I don’t know of any other agents exposed to almost 20,000 patients each in clinical trials. Most other agents were approved for marketing after trials involving a few thousand patients, and some corticosteroids now on the market had clinical trials involving a few hundred patients. In addition, prior to approval, infants were studied for a registration trial on topical pimecrolimus, and there are now data on several thousand infants who have been treated with that drug.

Second, if clinicians are not convinced by data from clinical trials, there are good human exposure data. As I mentioned before, approximately 5 million patients have been treated with pimecrolimus, and more than half of these were children. About 1.7 million have been treated so far with tacrolimus, and approximately one third of these patients are children. This is not an insubstantial number of patients.

**DR GUINAN:** I agree, but I suspect that some clinicians haven’t considered the points you raise.

**DR EICHENFIELD:** One of the problems is that many nondermatologists are reluctant to use corticosteroids, and this has resulted in a large number of cases of undertreatment of atopic dermatitis. This is one reason why the topical calcineurin inhibitors were so readily embraced by clinicians. Now, the inappropriate fear of calcineurin inhibitors that we are seeing has greatly added to the problem of undertreatment of patients.

**DR LEYDEN:** The FDA has taken a strong stand that they believe calcineurin inhibitors should not be first-line.

**DR ORLOW:** But the question is one of interpretation also, because the way the label originally read—and still reads—is that these medications essentially are to be used when either conventional therapy is ineffective or when the risks of conventional therapy would outweigh its use.

What about giving several days of oral corticosteroids to children with atopic dermatitis to treat an acute flare? I think it’s important to recognize that there have been no trials whatsoever examining the use of oral corticosteroids for the treatment of atopic dermatitis. There are no trials showing either safety or efficacy, yet we know they work.

**DR LEYDEN:** Yes, we do know they work.

**DR ORLOW:** The downside is the risk for rebound flares when the drug is stopped. Most of us have had patients with severe atopic dermatitis and have treated them with cyclosporine or phototherapy when the disease is bad enough. In the United Kingdom, azathioprine has been used, and studies have been done on the efficacy and safety of this drug in both children and adults with atopic dermatitis.

None of these agents is approved for this indication, but what do you do when a patient’s disease is very severe? I certainly have patients with atopic dermatitis in whom I use cyclosporine A because otherwise the patients would have no quality of life. Some of these patients have almost 100% body surface area involvement, with recurrent skin infections; they need the treatment. Obviously, I am much more circumspect about treating a patient with oral cyclosporine than I am about using almost any topical agent. When it comes to phototherapy, I think that from the pediatric standpoint, UVB has stood the test of time—it has been around for 100 years, and the risk for squamous cell carcinoma seems to be quite small. In contrast, the evidence with PUVA is that it is photocarcinogenic.

**Treatment of Infants With Atopic Dermatitis**

**DR ORLOW:** Since we are on the subject of off-label use of calcineurin inhibitors, what about the treatment of children under 2 years of age? What choices are available for on-label treatment of infants with atopic dermatitis? To my knowledge, there is fluticasone, now approved for treatment down to 3 months of age for up to 4 weeks, and there is prednicarbate for up to 4 weeks for babies from 1 year of age and up. These may be the only topical corticosteroids that are approved for use in children under 2 years of age, and, even then, their...
approved use is limited to 4 weeks. There are no long-term data on either of these agents.  

**DR GUINAN:** Is the approved time limit of utilization on those drugs commonly recognized among clinicians?  

**DR EICHENFIELD:** No.  

**DR ORLOW:** There are ongoing, long-term studies in infants on topical pimecrolimus.  

**DR EICHENFIELD:** Yes, and this drug is approved in more than 30 countries around the world for children under 2 years of age.  

**DR LEYDEN:** Are there data on the use of topical tacrolimus in children under 2 years of age?  

**DR ORLOW:** None prior to approval, but there has been subsequent infant exposure. I don’t know that any registration trials are planned. However, if clinicians restricted themselves to the indicated use of medications in infants, they would not be able to treat atopic dermatitis or some other conditions, such as asthma. In the case of both topical corticosteroids and topical calcineurin inhibitors, when it comes to infants, we are treating off-label, keeping patient safety high in our minds.  

**Black Box Warnings in Dermatology**  

**DR ORLOW:** Very few dermatologic medications have black box warnings. An example that is analogous to topical calcineurin inhibitors is tretinoin. Oral tretinoin, given to patients with leukemia, carries such a warning, whereas the topical form used to treat acne, does not. Another example is systemic metronidazole, which carries a warning about cancer in its labeling, whereas topical metronidazole does not. With these drugs, we recognize that there is a disconnect between the topical application of the drug and the systemic use of the medication.  

The same applies to calcineurin inhibitors, and there should be no change in the rules determining the evaluation of dermatologic drugs. If every dermatologic drug were to be judged according to the results of its being administered orally in animals, this would be extremely problematic. It is doubly problematic in the case of calcineurin inhibitors, for example, if the data are ignored and a body of clinicians decides that because the oral drugs may be related to the development of IRLD, topical administration increases the risk for IRLD. Mechanistically, this just does not make sense.  

**DR GUINAN:** In light of those comments, perhaps it would be useful to emphasize that, based on their understanding of the Health Advisory from the FDA, clinicians have become concerned that there are new data on infections that reflect a previously unrecognized problem. Actually, there is no new information at all, and, in fact, clinical experience seems to have shown that infections are not a significant issue. Clinicians have developed a comfort level in using topical pimecrolimus and tacrolimus, and, suddenly, old news about infections has caused a panic.  

**DR ORLOW:** The only real piece of current news is the addition to the reporting system of the case reports of lymphoma. I would also point out that the original package inserts for the topical calcineurin inhibitors contain much of the information that would be included in the proposed black box warning.  

**DR LEYDEN:** Right, so the addition of a black box would not be helpful to clinicians or patients.  

In addition to the black box, the Advisory Subcommittee voted 15 to 1 to recommend the distribution of a medication guide for patients using topical calcineurin inhibitors, indicating that children who have these medications applied to their skin may develop cancer. This kind of a document certainly would not be in the best interest of patients and would make it even more difficult to prescribe calcineurin inhibitors.  

**DR ORLOW:** And the labeling of topical medicines with black boxes is almost unheard of. I can think of no example of a black box based solely on animal data. And the recommendation for a medication guide is really over the top. I tried to determine what other drugs have medication guides, and they include oxycodone, oral isotretinoin, systemic interferons, and mefloquine, the antimalarial associated with an increased risk for violent psychiatric symptoms. Interestingly, oral cyclosporine does not have a medication guide. How can a medication guide possibly be justified for topical calcineurin inhibitors?  

Another result of the fear factor is that many patients and even clinicians believe either that the topical calcineurin inhibitors have been withdrawn from the market or that the FDA has proposed that they be withdrawn. This was never even considered.  

**DR LEYDEN:** In fact, the FDA made a statement that they were not even considering removing these drugs from the market because these are important drugs. They just wanted to be sure that the drugs were used appropriately.  

**Referral to a Dermatologic Specialist**  

**DR LEYDEN:** When should patients be referred to dermatologists? What is your recommendation?  

**DR ORLOW:** Nondermatologists should refer when they have used the medications with which they are familiar and comfortable, but the disease has not been readily well controlled.  

**DR LEYDEN:** Many nondermatologists are afraid to use topical corticosteroids, and now many clinicians, regardless of specialty, are cautious about topical calcineurin inhibitors. What’s left to treat atopic dermatitis? Most clinicians should feel comfortable with all but the highest-potency topical corticosteroids, and with calcineurin inhibitors. We feel comfortable that these drugs can be used safely. As the treatment algorithm on page 12 shows, we consider both topical corticosteroids and topical calcineurin inhibitors as having a place in the treatment of infants and young children. Both classes of topical drugs can be used safely, and the vast majority of patients will respond satisfactorily. Those who don’t should be referred to a dermatologist for further evaluation.  

**Conclusion**  

**DR LEYDEN:** The consequences of the publicity and news coverage resulting from the FDA’s Health Advisory on the topical calcineurin inhibitors led to serious concern and a reluctance on the part of many pediatricians and some dermatologists to continue prescribing these drugs.
a cancer risk and, incredibly, she wanted medicaments because of her belief about his eczema. She had stopped the topical came out, the patient’s mother called to application to his body and pimecrolimus I was able to get him down to about 3 mg/kg/day of the oral medication by prescribing topical tacrolimus for application to his body and pimecrolimus for application to his face.

He was doing well on that regimen, but about 2 weeks after the health alert came out, the patient’s mother called to say that he was having a severe flare of his eczema. She had stopped the topical medications because of her belief about a cancer risk and, incredibly, she wanted to know if I could increase his dose of oral cyclosporine instead so that her child would not be at risk. These are the kinds of situations clinicians are facing. DR LEYDEN: This is the problem in a nutshell. So what’s the solution? DR ORLOW: Clinicians should familiarize themselves with the data, consider the facts, and arrive at their own conclusions. I believe clinicians should treat patients who need treatment and explain the risks and benefits to them and/or to their parents.

DR LEYDEN: I think the simple message is that topical calcineurin inhibitors are safe and effective as approved and indicated, and there is nothing new to suggest otherwise.

References
Current Issues in the Management of Atopic Dermatitis in the Pediatric Patient

CME Post-Test and Evaluation

Release Date: September 2005  Expiration Date: September 30, 2006  Estimated Time to Complete This Activity: 2.0 Hours

CONTINUING EDUCATION INSTRUCTIONS: There is no fee to participate in this activity. Please forward the Test Answer Sheet and Evaluation form to: Elsevier Office of Continuing Medical Education, Department 290044, 685 Route 202/206, Bridgewater, NJ 08807 FAX: (800) 201-7217. Responses for AMA/Physician’s Recognition Award credit must be submitted by September 30, 2006.

INSTRUCTIONS: Circle the most appropriate response. Seven of 10 correct responses are required for credit.

1. Studies of topical calcineurin inhibitors in hairless mice demonstrated:
   a. A robust signal that these agents inhibit in vivo DNA repair
   b. No statistically significant difference between mice treated with pimecrolimus and the control group treated with vehicle only
   c. Strong evidence that tacrolimus causes skin cancer
   d. Strong evidence that these agents cause skin cancer when the mice were exposed to ultraviolet light

2. In the development of the topical forms of the calcineurin inhibitors:
   a. Primate studies demonstrated that use of these agents increases the risk for lymphoma
   b. Primate studies demonstrated that use of these agents increases the risk for nonmelanoma skin cancers
   c. Primate studies implied, but did not provide strong evidence, that use of these agents increases the risk for cancers, including nonmelanoma skin cancers and lymphoma
   d. No primate studies were done

3. Atopic dermatitis first appears in babies under 1 year of age in approximately _____ of cases.
   a. 25%
   b. 30%
   c. 55%
   d. 60%

4. The prevalence of atopic dermatitis is:
   a. Migrating into an older population
   b. Decreasing
   c. Increasing
   d. Decreasing in children but increasing in teenagers and adults

5. The foundation of any short- or long-term treatment or maintenance regimen is good bathing technique and:
   a. Emollient moisturizers
   b. Topical calcineurin inhibitors
   c. Topical corticosteroids
   d. Ultraviolet B light therapy

6. The final manifestation of the atopic march typically is:
   a. Allergic rhinitis
   b. Asthma
   c. Atopic dermatitis
   d. Food allergies

7. Atopic dermatitis is more likely to be confused with other conditions, especially:
   a. Psoriasis
   b. Early stages of cutaneous T-cell lymphoma
   c. Cutaneous B-cell lymphoma
   d. Fungal infection of the skin

8. Placebo- or vehicle-controlled clinical studies of topical calcineurin inhibitors have shown, after adjusting for time on trial:
   a. A non-significant increase in systemic infections
   b. A statistically significant increase in systemic infections
   c. No evidence of an increase in systemic infections
   d. A decrease in systemic infections

9. Low blood levels of topical calcineurin inhibitors are:
   a. Associated with immunosuppression
   b. Associated with immunosuppression during long-term treatment
   c. Associated with immunosuppression when used in combination with corticosteroids
   d. Not associated with immunosuppression, regardless of treatment duration

10. Available data suggest that the combination of a topical calcineurin inhibitor and a topical corticosteroid:
    a. Is superior to either agent alone
    b. Is superior to monotherapy but is associated with more adverse events
    c. Offers little or no benefit, compared to treatment with a single agent
    d. Appears useful in adults but not children with atopic dermatitis

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