



June 2008: VOLUME 1, NUMBER 8

Topical Calcineurin Inhibitors: Update on Safety



In this Issue...

In December 2000, the Food and Drug Administration approved the use of the first topical calcineurin inhibitor (TCI) tacrolimus 0.03% ointment for use in children over 2 years old, and tacrolimus 0.03% and 0.1% ointment in adults over 16 years, for the treatment of severe atopic dermatitis (AD). Approval for pimecrolimus 1% cream for treatment of moderate atopic dermatitis in patients over 2 years old followed in December 2001. Evidence-based literature demonstrated that these agents were safe and effective additions to the atopic dermatitis armamentarium.

However, in 2004, with rare cases of malignancy reported in patients treated with TCIs, the Pediatric Advisory Committee recommended that the FDA issue a Public Health Advisory regarding the safety of TCIs. In January 2006, the FDA instituted a mandatory black box warning on the packaging of both agents.

In this issue we review the recent evidence-based data on the use, efficacy, and safety of the TCIs.

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Release Date

June 26, 2008

Expiration Date

June 25, 2010

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August 7, 2008

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Guest Faculty Disclosures

Dr. Cohen has indicated a past and current financial relationship with Novartis, Pharmaceuticals, Astellas Pharma Inc., Medicis and Connetics. He served on the Speaker's Bureau for Novartis, Pharmaceuticals, Astellas Pharma Inc., and Medicis. He has also received grants for studies from Novartis, Pharmaceuticals and Astellas Pharma Inc. and received support for a fellowship program from Connetics.

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The authors have indicated that there will be no reference to unlabeled or unapproved uses of drugs or products in this presentation.

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Discuss with colleagues the most recent data on clinical efficacy of TCI's in the management of adults and children with atopic dermatitis
- Describe to colleagues the evidence of association between TCI exposure and non-melanoma skin cancer
- Describe to colleagues the evidence of association between TCI exposure and lymphoma

COMMENTARY

The TCIs offer the first new prescription non-steroidal medication alternative in our armamentarium for treating AD in adults and children in a generation. There are well-designed and executed evidence-based studies which demonstrate the efficacy of this class of drugs dating back to the mid-1990's in Europe and the United States, and convincing safety data is discussed in several of the studies (Margolis, Arellano, Qureshi, and Orlow) reviewed herein.

The 2004 FDA-issued Public Health Advisory to health care providers regarding the safety of TCIs stated, in part, that the "long-term safety of topical calcineurin inhibitors has not been established. Although a causal relationship has not been established, rare cases of malignancy (eg. skin and lymphoma) have been reported in patients treated with TCIs ... Therefore continuous long-term use of TCIs ... in any age group should be avoided, and application limited to areas of involvement with AD ... (Neither agent) is indicated for use in children less than 2 years of age." The advisory went on to recommend the use of TCIs only as "second line therapy for short-term and non-continuous chronic treatment ... in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable."

This move by the Pediatric Advisory Board and the FDA was likely prompted by a dramatic increase in off-label use of TCIs, which may have been precipitated by aggressive marketing to both primary care providers and consumers. The risk of cancer was based on the known immunomodulatory effects of the systemic calcineurin inhibitors and the concern of systemic absorption, particularly in children under 2 years old. Anxiety was further increased by selected animal data and case reports of malignancy in TCI clinical and post marketing studies.



When the mandatory black box warning on the packaging of both agents was instituted in January 2006, a number of national and international medical societies engaged in public discussion of the safety and efficacy of the TCIs. The American Academy of Dermatology, the Canadian Dermatology Association, and the American Academy of Allergy, Asthma, and Immunology advocated for reconsideration of the black box warning. In spite of lobbying by pediatric dermatologists in the American Academy of Pediatrics, the AAP failed to take a position on the TCIs.

The advocacy groups argued that the TCIs were approved by the FDA after consideration of safety and efficacy studies in 38,000 patients, including 14,000 children less than 17 years of age. They emphasized that there was no evidence of an increased rate of lymphoma when compared to data from the general population in the Surveillance Epidemiology and End Result Database. Moreover, the clinical and histologic patterns in the cases of lymphoma reported in patients treated with TCIs were not consistent with typical immunosuppression-related lymphomas. Multiple studies 1-7 showed no evidence of significant absorption of TCIs in short-term continuous or long-term intermittent treatment of AD in adults and children, and there was no evidence of interference with the effectiveness of immunization and delayed hypersensitivity skin responses or increased rate of systemic infections.

The FDA, National Eczema Association, and the preceding advocates of the TCIs acknowledge that this novel class of medications requires continued study, and that patients need close long-term monitoring. The TCI manufacturers, with the encouragement of the FDA, are supporting 10 year safety studies to generate additional safety data, which should be available by 2016.

At the present time, TCIs should be used in the context of a complete treatment regimen. The potential risks and benefits should be discussed carefully with parents and patients, and when the decision is made to prescribe a TCI, a discussion of the black box warning should be undertaken. Off-label use of the TCIs, particularly in children less than 2 years old, should be done judiciously. Controlled studies of the use of TCIs and topical steroids, as well as other agents, should be sponsored in adults and children with AD, particularly those less than 2 years of age.

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AD TRENDS AND Rx PATTERNS

Horii KA, Simon SD, Liu DY, Sharma V. **Atopic Dermatitis in Children in the United States, 1997-2004: Visit Trends Patient and Provider Characteristics, and Prescribing Patterns**. *Pediatrics*. 2007;120(3):e527-e534.

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The aim of this study was to describe trends in visits for AD in children up to 18 years old in the United States between 1997 and 2004, examine factors that were associated with

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the diagnosis of AD, and to assess changes in the treatment of AD over this period. The authors performed a retrospective, cross-sectional study of outpatient encounters compiled by the National Ambulatory Medical Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) databases from 1997 through 2004. The information for the NAMCS was collected from non-federally funded, community, office-based physician practices throughout the United States. NHAMCS includes data on patient visits to hospital outpatient clinics and emergency departments. The data from both databases represented a proportion of visits, not a proportion of patients, because they track visits and not individual patients

Patients from 0-18 with a diagnosis of AD in primary and secondary diagnosis fields were included. Topical medications were identified by using the National Drug Code Directory. Over-the-counter medications were excluded. Statistical analysis was performed using Stata software as recommended by the Ambulatory Care Statistics Branch of the Centers for Disease Control and Prevention National Center for Health Statistics (NCHS). Ninety-five percent confidence intervals for all counts and proportions were estimated. For events in which the sample size was small, the time variable was split into two 4-year intervals, 1997-2000 and 2001-2004.

Among the key findings the authors report:

- There were 7.4 million visits for AD in children up to 18 years of age in the United States between 1997 and 2004. There was a dramatic increase in visits from 1997 (620,000) to 2003 (1.7 million), while the number of pediatric visits was stable during the period.
- From 1997 to 2000 there were a total of 2.8 million AD visits, with 0.9 million (34%) involving a prescription of topical steroids. The number of visits for AD from 2001 to 2004 increased to 4.6 million, with 25% involving a prescription for a topical steroid (not a statistically significant decline). Fourteen percent and 21% involved a prescription for antihistamines (also not a statistically significant difference). In 2001 to 2004 prescriptions for 10% and 13% of encounters were written for topical tacrolimus and pimecrolimus, respectively for a total of 23% of visits.
- Among children less than 2 years of age, there were 0.7 million visits from 1997-2001 and 1.3 million visits from 2001 to 2004. During these visits, 21% and 24%, respectively, involved a prescription for a topical corticosteroid which was not statistically different for the periods. Antihistamines were written in 7% and 18% of visits, respectively. Topical tacrolimus was prescribed in 8% and topical pimecrolimus in 14% of visits for children less than 2 years of age from 2001 to 2004.

The authors demonstrate a clear increase in the number of visits for AD, which they call a surrogate measure of the increased prevalence in AD in the United States during the time of the survey. They authors also recognize the impact of moderate to severe AD on quality of life for children and their families, and, specifically, note sleep disturbances, anxiety levels, and maternal depression, which exceed that for caring for children with chronic asthma and diabetes.) These issues coupled with the increased diagnosis of AD are important factors in the search for more effective treatment options and particularly non-steroidal alternatives.

Although they note that topical steroids are recommended as the primary treatment for AD, their study found that oral steroids were actually prescribed for initial therapy in one-sixth of visits and TCIs in a quarter of visits, including visits for children less than 2 years of age. They conclude that there is a need for more clinicians to provide care for patients with AD, and closer safety monitoring because of the high prevalence of off-label use of TCIs and other agents.

TCI USE & SKIN CANCER IN ADULTS

Margolis DJ, Hoffstad O, Bilker W. **Lack of association between exposure to topical calcineurin inhibitors and skin cancer in adults.** *Dermatology*. 2007;214(4):289-295.

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The objective of this case-controlled study was to determine if there is an increased risk of nonmelanoma skin cancer (NMSC) in patients who have used TCIs. Five thousand eligible

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adults with a history of AD, recruited from faculty clinics at the University of Pennsylvania Department of Dermatology between 2002 and 2005, were asked to complete a questionnaire by mail. Eligible patients were 30 years of age or older and had received a diagnosis of AD at their initial evaluation by full-time faculty. They were excluded from the study if they were initially referred for evaluation and/or treatment of skin cancer. Study cases were randomly selected from eligible patients if they were diagnosed with NMSC at subsequent visits during the study period. Control patients were randomly selected from eligible patients if they had a subsequent visit for dermatitis and did not have a diagnosis of NMSC during the study period.

The primary study variable was exposure to topical pimecrolimus, tacrolimus, or both. Patients with a history of exposure to systemic calcineurin inhibitors or other immunosuppressive medications were excluded. Data on potential confounders that could be associated with an increased risk of NMSC (eg. history of previous illness, age, skin type, ethnicity, prior history of skin cancer, history of smoking, history of sunburn, past use of medications) was also obtained and carefully controlled during statistical analysis.

The survey included 1000 study subjects with NMSC and 4000 controls, with the investigators receiving responses from 70.7% of those surveyed. 25.7% of subjects reported using TCIs, with usage similar in the study and control groups. Specifically, TCI exposure was 14.4% for cases and 30% for controls. The nonadjusted odds ratio was 0.38 with confidence limits of 0.31-0.47 and adjusted odds ratio (for age, gender, previous NMSC, history of AD) was 0.54 with confidence limits of 0.41-0.69. The odds ratio actually decreased as the number of tubes of TCIs used increased.

Based on data from systemic agents the investigators had predicted at least a small increase in NMSC because of the potential for systemic absorption with use of the TCIs. However, they found that there was no increase in risk of NMSC and, perhaps, even a small decrease in risk.

The selection of patients for this study was felt to be uniform because the diagnosis of AD and NMSC was made by dermatology faculty and confirmed by skin biopsy (NMSC). Potential limitations of this case-control study include selection bias; however, careful selection of cases and controls, as well as adjustment for confounders, makes this less likely. Further, information and diagnosis bias was minimized by using data from dermatologists rather than primary care providers. Recall bias by subjects who had used TCIs would have resulted in underestimation of the negative association.

The investigators admit that this study was performed only 3-4 years after introduction of the TCIs, and experience with systemic calcineurin inhibitors suggests that 2-10 years of immunosuppression may be required before patients present with increased numbers of NMSC. As a consequence, they plan to study a new group of patients in 2010. Of note, one of the authors was on a scientific advisory board for Astellas, which had no knowledge of this study.

TCI USE & LYMPHOMA

Arellano FM, Wentworth CE, Arana A, Fernandez C, Paul CF. **Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis.** *J Invest Dermatol.* 2007;127(4):808-816.

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Using a design similar to the NMSC study described above by Margolis et al, these investigators performed a nested case-control study in the PharMetrics database to evaluate the association between topical immunomodulators (TCIs and corticosteroids) and lymphoma in patients with AD. The PharMetrics database incorporates information from 43 million patients from 73 health care plans and is representative of the United States managed care population. Diagnostic codes 691 and 692 were used to identify patients from 1995 to 2005 with a diagnosis of dermatitis. Only patients who were entered into the database for at least 6 months were included in the data analysis. Of the 293,253 patients eligible: 171,724 were less than 20 years of age, 75.4% entered the database from 2001 onwards, 60% were female, 20% were categorized as severe, and most were diagnosed by family doctors, pediatricians, or dermatologists.

25% of patients were using topical steroids, and 3% and 1.5%, respectively, were using topical pimecrolimus and tacrolimus at entry into the database. At follow-up, half of the patients were not using any medications, 40% were using topical steroids, and 12% were

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exposed to TCIs.

A total of 294 lymphomas occurred after the index date, 81 (27.6%) developing in subjects less than age 20, for an incidence rate of 81 per 100,000 person-years. The numbers of cases exposed to pimecrolimus, tacrolimus, or both were 14, 11, and 5, respectively. In two-thirds of patients, the type of lymphoma was unknown; the breakdown for those lymphomae which were identified included Hodgkin disease in 11.2%, non-Hodgkin lymphoma (NHL) 22.8%, B-cell NHL 4.4%, and T-cell NHL 18.4%.

The odds ratios for lymphoma risk for AD patients over age 30 were increased, especially for those over age 60 (OR 9.7, 95% CL 4.7-19.8). The risk for males and females was equal, but the risk was elevated for patients from the Eastern United States (OR 2.1, 95% CL 1.5-2.9) compared to the Midwest. Severe AD (OR 3.1, 95% CL 2.1-4.5), visits to dermatologists or allergists in comparison to family practitioners, and use of oral steroids and/or super-high potency topical steroids were also associated with an increased risk of melanoma.

The incidence rate of 81/100,000 person-years in adult patients with AD is compatible with the 2-3 fold increased risk reported in other studies. No increased risk was noted for those patients who were treated with TCIs. The increased risk of lymphoma associated with the use of oral steroids and high potency topical steroids virtually disappeared when the data were controlled for disease severity. The 2-3 fold increased risk of lymphoma is consistent with the increased risk of lymphoma reported in patients with other severe chronic inflammatory disorders such as rheumatoid arthritis and psoriasis.

The main strength of this study was the large sample of AD patients. The risk of confounders was minimized by performing the analysis nested in a cohort of patients with AD. The primary limitation was the inability of the investigators to validate information obtained by record linkage in the PharMetrics database. Additionally, there is no data on the use of over-the-counter medications in these patients. Finally, the study was based on a relatively small number of lymphoma cases with relatively short follow-up and exposure times.

Although the study was well conceived and executed, clinicians should note that it was sponsored by Novartis (the manufacturer of pimecrolimus), one author was a paid consultant for Novartis, and 2 authors were employees of Novartis. However, the authors and Risk Management Resources had complete control over data analysis, content of the paper, and selection of the journal for publication.

PHARMACOKINETICS OF TACROLIMUS

Krueger GG, Eichenfield L, Goodman JJ, et al. **Pharmacokinetics of tacrolimus following topical application of tacrolimus ointment in adult and pediatric patients with moderate to severe atopic dermatitis.** *J Drugs Dermatol.* 2007;6(2):185-193.

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The objective of this paper was to characterize the pharmacokinetics of tacrolimus after topical application in adult and pediatric patients with moderate to severe AD. The data were reported from 2 pharmacokinetic trials and 12 efficacy trials of tacrolimus ointment. These trials were supported by Astellas Pharma US; 6 of the authors were full time employees of Astellas, and 2 have been clinical investigators for Novartis. Clinicians should note that studies like this have been encouraged and required by the Food and Drug Administration as part of continuing investigations into the safety and efficacy of the TCIs.

The adult and pediatric pharmacokinetic studies were open-label studies sized to generate adequate data to characterize the pharmacokinetics of tacrolimus after application. In the adult study, subjects with AD who were over 16 years old were assigned to apply tacrolimus 0.03% or 0.1% for 12 weeks. In the pediatric study, children over 2 years old and less than 6 years old applied tacrolimus 0.03% for 2 weeks. Tacrolimus was applied twice daily to all areas of involvement regardless of the response to therapy, and new lesions were also treated for the duration of the studies. The condition of the areas of skin being treated were monitored and recorded throughout the trials.

To be eligible subjects had to have had AD diagnosed (based on Hanifin and Rajka criteria) for at least 3 months; severity was also scored using these criteria, requiring 35%-75% of the body surface involved. Patients with Netherton's syndrome or other disorders



of epidermal barrier function, or who had used systemic immunomodulators or immunosuppressives during the prior 2 weeks, or topical or systemic steroids during the prior week, or tacrolimus in any form during the prior 2 weeks for adults or 30 days for children, were excluded.

Tacrolimus blood level data from 12 clinical efficacy trials were also analyzed. Ten of these trials were randomized, blinded, controlled trials of either 3 or 12 week duration, using twice daily application of either tacrolimus 0.03% or 0.1%. The remaining 2 trials were open-label studies of up to 1-2 years, with patients receiving twice daily applications of 0.1% ointment. Seven trials included adults only, 4 children only, and 1 both adults and children. In the efficacy trials, topical therapy was continued for a week after clearing of clinical lesions and restarted with recurrent disease — this protocol differed from the pharmacokinetic studies, in which the treatment continued even after clearing for the duration of the study.

In the pharmacokinetic studies, the lower limit of quantification (LOQ) was 0.1 mg/ml, with levels below considered to be zero for data analysis. The maximum concentration and time to maximum concentration were recorded. Systemic exposure to tacrolimus was calculated from the area under the concentration-time curve. In the pediatric study 15 whole blood samples were obtained, and 31 in the adult study. In the clinical efficacy trials the LOQ was 0.5 ng/ml (enzyme-linked immunosorbent assay) and repeated by mass spectrometry, giving a LOQ of 0.025 ng/ml. Blood samples were drawn periodically throughout the duration of the efficacy trials.

In the pharmacokinetic studies, 89-95% of the tacrolimus samples were less than 1 mg/ml, mean concentrations ranged from 0.2-1.6 ng/ml, and the mean area under the blood concentration curves ranged from 1.4-13.1 ng-hr/ml. The findings were similar in the clinical efficacy trials, with 85-99% of tacrolimus concentrations less than 1 ng/ml. By way of comparison, the mean area under the blood concentration curves in pediatric and adult solid organ transplant patients is generally over 100 times that for patients in the studies reported in this paper. Most of the samples in the pharmacokinetic and efficacy studies were below the lower LOQ.

The investigators concluded that topical tacrolimus, even in patients with severe disease that involved surface areas exceeding 50%, produced systemic absorption that was minimal, and that the drug did not accumulate despite applications up to 24 months.

BALANCING TCI BENEFITS & RISKS

Qureshi AA, Fischer MA. **Topical Calcineurin Inhibitors for Atopic Dermatitis: Balancing Clinical Benefit and Possible Risks.** *Arch Dermatol.* 2006;142(5):633-637.

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Following the FDA actions in January 2006, the National Eczema Association (NEA) commissioned two physicians at Brigham and Women's Hospital – dermatologist Abrar A. Qureshi, MD, MPH, and pharmacoepidemiologist Michael Fischer, MD, MS – to conduct a review of current data on the safety of TCIs, and to make recommendations for the use of these agents by practitioners and patients. The results of this report were subsequently published in an editorial in the Archives of Dermatology.

The authors emphasized the limitations of drug safety information from pre-marketing trials and post-marketing reporting, the inability of black box labels to give adequate instructions to practitioners toward better prescribing, the effects of aggressive marketing to practitioners and patients, increasing off-label use, and the lack of post-marketing safety data.

The NEA summarized the most important points of the report. They recognized the efficacy of the TCIs and the advantages of these agents over topical steroids in selected settings. The risk of absorption was assessed as minimal in most patients. However, there was concern about off-label use of the medications, recognition that sporadic reports are not a reliable source from which to infer safety, lack of long-term data from Phase IV studies, animal studies showing that when percutaneous absorption is high there is a significant risk of lymphoma, and delay in initiation of comprehensive long-term safety studies.

As a consequence, the investigators concluded that it would take another 5 to 10 years to generate enough safety data to understand a possible association between the use of

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TClIs and cancer; both the authors and the NEA requested close collaboration between all involved parties to ensure clinical follow-up and compliance with therapy.

[Editor's Note: A complete copy of this report can be reviewed in the May 2006 editorial section of the Archives of Dermatology and recommendations based on this report are summarized in a statement published on the NEA website, [available online](#).

ANALYSIS OF CURRENT TCI ISSUES

Orlow S. **Topical calcineurin inhibitors in pediatric atopic dermatitis: a critical analysis of current issues.** *Paediatr Drugs.* 2007;9(5):289-299.

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In this review paper, the author discusses critical summary data on potential immunosuppression and cancer risk in both human and animal studies. He makes a convincing case for the lack of immunosuppression when TCIs are compared to systemic use of calcineurin inhibitors in transplantation. In transplant patients, blood levels of these agents are high and sustained, resulting in sustained immunosuppression, and, particularly, T-cell inhibition. TCIs result in undetectable or transiently low levels in the blood, cause temporary suppression of hyperactive skin immune responses by inhibiting cutaneous T-cells in areas of active inflammation.

A causal relationship with systemic calcineurin inhibitors and lymphoma has been well established with typical clinical and histologic findings. The tumors are usually EBV positive B-cell lymphomas and typically respond to reduction in immunosuppression. There is a clear relationship to dose and exposure time. However, with TCIs, no causal relationship has been established, the tumors are not associated with EBV, discontinuation of the TCIs does not result in regression of the tumor, and there is no pattern of TCI use.

The author reviews animal data showing that the required dose to trigger tumor formation in several animal models exceeds the guidelines for testing of carcinogenicity of pharmaceuticals recommended by the International Conference on Harmonisation.

Risk of systemic immunosuppression was further assessed by a number of investigators who studied the effects of TCIs on the response of subjects to vaccinations, skin delayed-type hypersensitivity reactions, and the incidence of infections. There were no differences in seropositivity for tetanus, diphtheria, measles, rubella, and pneumococcal vaccines when children treated with TCIs were compared to untreated children. Recall antigen testing – including tuberculin, tetanus, Streptococcus, Candida, Trichophyton, and Proteus – were also similar in treated and untreated children. Further, a pooled analysis of adult and pediatric subjects from 5 clinical trials showed that the use of TCIs was not associated with an increased risk of bacterial and viral skin infections.

The author concludes by reassuring clinicians of the safety and efficacy of TCIs based on current data, and advocates for careful use of these agents when designing treatment regimen for long-term management of AD.

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Learning Objectives — [back to top](#)

At the conclusion of this activity, participants should be able to:

- Discuss with colleagues the most recent data on clinical efficacy of TCI's in the management of adults and children with atopic dermatitis
- Describe to colleagues the evidence of association between TCI exposure and non-melanoma skin cancer
- Describe to colleagues the evidence of association between TCI exposure and lymphoma

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