

Topical calcineurin inhibitors for atopic dermatitis: Balancing clinical benefit and possible risks

¹ Abrar A. Qureshi, MD, MPH and ² Michael A. Fisher, MD, MS

¹ Translational Resource Research Center, Department of Dermatology, ² Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Womens' Hospital, Harvard Medical School, Boston, MA

Competing interests: This report was funded by a grant from the National Eczema Association for Science and Education (NEASE) to AAQ. We are grateful to Professor Hywel Williams for his review and comments on the report. Dr. Qureshi and Dr. Fischer have never received direct funding from Novartis or Astellas.

Purpose: This report has been written by AAQ at the request of NEASE. The purpose of the report is to provide an objective, independent view of the evidence surrounding the effectiveness and possible side effects of topical calcineurin inhibitors in response to the recent Food and Drug Administrations (FDA) concerns. The report is meant for patients with atopic dermatitis and their providers.

Corresponding author:

Abrar A. Qureshi, MD, MPH
Instructor, Department of Dermatology
Brigham and Women's Hospital
Harvard Medical School
45 Francis Street, 221L
Boston, MA, 02115
617-525-7233
F 617-228-4634
aquireshi@partners.org

Layman's Statement

Atopic dermatitis (AD) is a common skin condition that affects a large number of people in the United States. These people often suffer with chronic unrelieved itching, broken and bleeding skin leading to insomnia, decreased productivity and low self-esteem. The mainstay of therapy is to keep the associated dry skin moisturized using emollients, to reduce skin inflammation using topical steroids over a long period of time, and to treat superimposed infection. In December 2000, the FDA approved tacrolimus (Protopic®) ointment, a non-steroid topical agent for use in AD. A year later, in December 2001, the FDA approved a second agent, pimecrolimus (Elidel®) cream for the same indication. Unlike topical corticosteroids, tacrolimus and Pimecrolimus do not cause thinning of the skin, redness, or development of stretch marks. There has been considerable interest among AD patients and physicians hoping that these new agents might be safer for the skin in the long term than topical steroids. However, their effects on other organ systems in the body and their long-term effects on skin are still not completely known since they have only been available for the last 5 years.

Adverse drug reactions (ADRs) are believed to be one of the leading causes of death in the United States. In recent years, increasing attention has focused on how ADRs are detected and what can be done to obtain better data on the risk of ADRs. In particular, the withdrawals of high-profile drugs led to questions about whether the Food and Drug Administration (FDA) could have appreciated the risk of serious ADRs earlier than it eventually did. Before the FDA approves a new drug, it is tested in clinical studies. These pre-approval studies are usually designed to demonstrate efficacy, not long-term safety, and use carefully selected populations, in which an effect of the drug is likely to be seen over a relatively limited period of time. Hence, safety data from pre-approval studies is really short-term safety data, especially for adverse effects such as cancer that can take many years to develop. After FDA approval, pharmaceutical companies can market drugs to patients and physicians. When a drug is approved, the FDA label will specify the clinical indication(s) for which the drug was tested and found to be effective. Once a drug is on the market, physicians can use it "off-label," prescribing the drug for a condition not included in the labeling information, or in patients with the approved indication who differ from the patients in the clinical trials, or for extended periods of time beyond those originally studied.

The FDA does not have the ability to restrict off-label prescribing and has a very limited capacity to gather data once a drug is on the market. The FDA does maintain a database of spontaneous reports of ADRs, but these data are generally not sufficient to draw firm conclusions about the association between a given drug and a clinical event that may be an ADR. Post-marketing surveillance studies (also known as Phase IV studies), examining use of the drug in the real world setting, offer the only way to evaluate long-term safety in an unbiased and systematic way without making drug discovery prohibitively expensive and time-consuming. When a drug is approved for marketing, companies generally make a commitment to the FDA to conduct Phase

IV studies. Unfortunately, recent reviews have revealed that over 70% of planned Phase IV studies have not even been started leaving a void in the long-term safety (<http://a257.g.akamaitech.net/7/257/2422/01jan20051800/edocket.access.gpo.gov/2005/pdf/05-3221.pdf>) data for many widely-used drugs.

In January 2005, just a few years after approving tacrolimus and pimecrolimus, the FDA raised concerns about use of these agents in AD, suggesting that there is a potential risk of cancer and recommending a “black box” warning. A “black box” warning is text written within a boxed line that explains the nature of risk associated with use of a drug. The warning must be displayed prominently in the package insert (information that accompanies the drug), Physicians’ Desk Reference materials, and all drug labeling, including brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, letters, exhibits, literature, reprints, as well as any other materials in audio, visual, or print matter form that describe the use of the drug by medical practitioners, pharmacists or nurses.

The goal of this report is to provide, for AD patients and the providers caring for them, an independent, unbiased and balanced perspective on the risks and benefits of tacrolimus and pimecrolimus. This report finds that the clinical efficacy data - used by the FDA to approve these agents for AD in 2000 and 2001 - support the continued use of tacrolimus and pimecrolimus in selected patients with AD. Practitioners prescribing these drugs need to be educated about and must understand that the specific nature of risk from these agents as a cause of skin cancer or lymphoma in any age group is unknown at this time. In most AD cases, these drugs should not be used as first-line therapy. The drugs are not indicated for use in children < 2 years age and off-label use in this age group is not recommended without compelling clinical reasons. The drugs are also not indicated for long-term preventive therapy of AD and prescribing should be limited in that regard. Use of large amounts of drug topically over large areas of diseased skin has been shown to increase systemic absorption. All patients being prescribed tacrolimus or pimecrolimus should be followed clinically and these agents should not be considered safe for indefinite use over extended periods of time. This report also expresses concern about prescribing patterns for both agents and how these have been influenced by promotion and marketing. There is also concern that much needed post-marketing surveillance studies that are part of the FDA requirements (regulatory commitment) have taken longer than would have been hoped to implement, with considerable time lost since approval of both drugs. Despite these concerns, the utility of adding a “black box” warning may not achieve the optimal clinical outcome, i.e. suitable care of the patient with AD. Use of this type of warning also will not guide clinicians toward better prescribing of these agents.

Clinical report

The morbidity of Atopic Dermatitis

Atopic dermatitis (AD) is a common skin condition that affects a large number of people in the United States and is often associated with atopy [1]. The majority of patients with AD have chronic itchy skin that has a poor barrier function, often with areas that are broken or bleeding due to scratching provoked by intractable itching [2]. Atopic dermatitis may be associated with allergies and asthma, and about 50% of patients with AD will develop asthma [3, 4]. Many AD sufferers are limited to some degree in their ability to participate fully in normal school, work, and social activities, but appropriate therapy can help prevent days lost.

The sub-population of AD patients with more significant disease suffer from severe skin involvement and associated complications that may require hospitalization and systemic therapy. More than one-fourth of all AD health care-related costs may be attributed to AD-related comorbidities [5]. Although not considered life-threatening, the skin breakdown observed in AD can predispose an individual to serious infections, with resulting complications that can be fatal in some very rare cases such as eczema vaccinatum as a complication of small pox vaccination [6]. For patients with severe AD the quality of life is significantly impacted, as are self esteem and social and interpersonal relationships[7-10]. For children with AD, some of the burden of disease falls on the parents. A method to study Parents' Index of Quality of Life in Atopic Dermatitis (PIQoL-AD) has also been developed and tested in Europe[11]. In such circumstances not only does the individual suffer from AD, the entire family is usually affected as well [12].

Although AD is considered a chronic non life-threatening condition, it has a significant impact on public health. The burden of atopic dermatitis can be measured on the individual level [8] and on the community level [14, 15]. Individuals suffering from atopic dermatitis may be severely affected, and the burden of illness is usually measured as impact on health-related quality of life [7]. Estimation of health-related quality of life is a scientific method to quantify the impact of AD across the large group of affected individuals. For individual patients and their families, however, daily events such as a child being turned away from a swimming pool due to visible sores on the skin from constant scratching may have as much impact as any specific symptom. It has been recommended that multidisciplinary care for these patients should also include psychosocial approaches [13]. The burden of illness on the community is usually measured as dollar costs in millions. In a recently presented joint study sponsored by the Society for Investigative Dermatology and the American Academy of Dermatology, atopic dermatitis was found to be in the top ten most prevalent skin diseases and had a total direct cost of \$1.47 billion (<http://www.sidnet.org>). In 2002, prescription drugs accounted for 47% of this expense. According to the same report, lost productivity due to AD was estimated at \$635 million in 2002, including \$166 million in lost work days.

Therapy of atopic dermatitis

Therapy is important to maintain normal skin function, but treatment options are limited. The mainstay of therapy is to reverse associated dryness with emollients, reduce skin inflammation and treat superimposed infection over a long period of time. A comprehensive approach to the AD patient includes evaluation of potential triggers and education of the patient and family regarding proper avoidance of such triggers. Hydration of the skin and maintenance of an intact skin barrier remain integral to proper management. Topical steroids have been effectively used for around 40 years. Long-term use over large areas of inflamed skin may result in systemic absorption and suppression of the hypothalamic-pituitary axis may occur. Local adverse effects include epidermal and dermal atrophy, with consequent appearance of prominent telangiectasia, striae and dyspigmentation. If the topical steroids are applied to the peri-ocular areas for extended periods of time, ocular adverse effects including cataract formation and increased intra-ocular pressure may develop. Lower potency topical steroids may be used with few adverse effects on the face and intertriginous areas. Although safer, lower potency topical steroids do not have the same efficacy as their more potent counterparts. Frequency of application, pulsed therapy versus continuous therapy and maintenance therapy to prevent relapse have been issues addressed in previously published work. It is generally recommended that one application per day to affected areas is used, with twice or three times a week therapy to prevent flares and choice of the least potent topical steroid that has efficacy for the individual patient.

Topical steroids have both skin and systemic side effects. These agents have been used for a few decades in a variety of skin conditions including atopic dermatitis, with use in both children and adults and in varying potencies and adverse events have been reported [16-19]. Due to this long-term practical experience, most clinicians are comfortable prescribing topical steroids. Systematic Phase IV studies have not been conducted with topical steroids and, as with many older medications good data on long-term safety of topical steroids are not available.

Topical calcineurin inhibitors (TCIs) are a new class of agents approved by the Food and Drug Administration for the treatment of AD. Both pimecrolimus (Elidel®) and tacrolimus (Protopic®) inhibit calcineurin in T lymphocytes and prevent T cell proliferation via reduction of several pathways including inhibition of interleukin-2 (IL-2) production. Systemic tacrolimus was originally developed for immunosuppressive use in solid-organ transplant patients to prevent host rejection of the grafted organ, then was subsequently evaluated as a topical agent. Like topical steroids, the topical calcineurin inhibitors improve the health-related quality of life of children and adolescents as well as the QOL of parents of children with atopic dermatitis. Furthermore, they do not cause skin atrophy or ocular problems as topical steroids can. The acute side effects are burning and itching, and these decrease with improvement of AD. As mentioned above regarding topical steroids, the long-term side effects of TCI's are largely unknown. Although unfortunately delayed a few years

since approval for both drugs, formal Phase IV studies have recently been initiated, and should provide more data in the coming years.

FDA concerns about topical calcineurin inhibitors

The FDA has recently raised concerns about use of tacrolimus and pimecrolimus in AD individuals, suggesting that there is a potential risk of skin cancer in adults and lymphoma in children and recommending adding a “black box” warning. It is not clear that the amount of data available since approval is sufficient to draw causal associations between drug use and cancer occurrence at the present time. Widespread use of these agents as first-line and long-term topical therapy for AD in children and adults is of concern and is related to the manner in which the drugs have been marketed. The conscientious clinician caring for patients with AD is left in a difficult position, trying to navigate between marketing claims on one hand and dire FDA warnings on the other. This report will evaluate both the efficacy data and the ADR data that have caused the FDA to consider a “black box” warning and will respond to clinicians and AD sufferers with new recommendations based on an independent expert review.

Efficacy data and short-term tolerability of topical calcineurin inhibitors

Topical calcineurin inhibitors (TCI) have been evaluated in randomized controlled trials (RCTs) comparing either drug to placebo or to topical steroids. Skin-related adverse events in treated versus placebo or untreated patients were mainly related to discomfort when TCI were initially applied, e.g. burning and itching [20, 21]. Adverse effects seen with topical steroids such as redness, acneiform eruptions, skin atrophy and pigmentation changes were not seen at an increased rate in patients treated with TCIs.

A systematic review was conducted to determine the efficacy and tolerability of topical pimecrolimus and tacrolimus [21]. Of a total of 6,897 participants in 25 randomized controlled trials, 4,186 received pimecrolimus or tacrolimus. Both topical agents were found to be more effective than placebo. For example, for 33% of patients treated with pimecrolimus the skin became clear or almost clear, versus 10% on placebo (number needed to treat (NNT) = 5).

Tacrolimus 0.1% was as effective as potent topical corticosteroids at three weeks and more effective than combined treatment with hydrocortisone butyrate 0.1% (moderate potency) plus hydrocortisone acetate 1% (lower potency) at 12 weeks (NNT = 6) [22]. Tacrolimus 0.1% was also more effective than hydrocortisone acetate 1% (NNT = 4). In comparison, tacrolimus 0.03% was more effective than hydrocortisone acetate 1% (NNT = 5) but less effective than hydrocortisone butyrate 0.1% (NNT = -8). Pimecrolimus was far less effective than betamethasone valerate (high potency topical steroid) 0.1% (NNT = -3 at three weeks). When pimecrolimus was compared to tacrolimus 0.03%, it was less efficacious (NNT = -9). Pimecrolimus and tacrolimus caused more skin burning than topical corticosteroids. Rates of skin infections were not found to be different.

In summary, both topical pimecrolimus and topical tacrolimus are more effective than placebo treatments for atopic dermatitis. Topical tacrolimus is similar to potent topical corticosteroids and the efficacy data suggest that it may have a place for use in patients with AD on sites where side effects from topical corticosteroids might develop quickly or for selected other patients such as those who are steroid non-responsive or have contraindications to steroids. In the absence of key comparisons with mild corticosteroids, and concern about possible risks, the clinical need for topical pimecrolimus may be more restricted to specific AD patients who are not responsive to topical steroids or have other clinical circumstances e.g. a patient with AD who has developed stretch marks due to topical steroid use. Hence, from an efficacy perspective, bearing in mind potential unknown risks, both topical calcineurin inhibitors have a place in the therapeutic armamentarium, but not as first-line therapy and with considerably more focused and restricted prescribing than has been the case to date.

Systemic adverse effects of topical calcineurin inhibitors

Topical application of any agent will result in some systemic absorption, and this is true for both steroids and calcineurin inhibitors. When the skin is inflamed, the barrier function is not optimal. Hence, application of the same agent at the same concentration can result in more systemic absorption that would have occurred if the skin was not inflamed.

Adrenocortical suppression (i.e. inhibition of the hypothalamic-pituitary axis) is a potential complication of the use of topical corticosteroids in patients with AD [23, 24]. Topical application of tacrolimus and pimecrolimus also results in systemic absorption, although the serum concentrations of the drugs are not at clinically significant levels in the majority of patients [25]. As in the case of topical steroids, when the AD improves the systemic absorption decreases. The therapeutic range for tacrolimus in organ transplant recipients is 5 to 15 ng/ml and the lower limit of detection in peripheral blood is 0.5 ng/ml [26, 27]. In two clinical trials in adults, involving 631 adults, the majority of patients (about 80%) using topical tacrolimus had no detectable levels and concentrations > 5 ng/ml were found in 3 participants, with the highest level being 8.13 ng/ml [27, 28]. In a pediatric study with 351 atopic children, > 90% had no detectable levels [29]. However, the highest detectable level was 2.28 ng/ml in one participant. The highest blood levels resulting from topical tacrolimus therapy were demonstrated in a study by Kawashima et al [30]: in patients with severe AD receiving daily application of large amounts of tacrolimus (>10 gm per day, or roughly 3-5 times the dose that would be used normally) 2 of 17 subjects had blood levels of 20 ng/ml .

Lymphoma in animals

In non-human primates, a 30 times maximum recommended human dose (MRHD) of an oral version of pimecrolimus was associated with lymphoma (Novartis and Fujisawa (now Astellas) briefs at FDA PAC). However, this was an oral formulation at a high dose. Topically applied pimecrolimus and tacrolimus in ethanol at 47x and 26x MRHD in mice was associated with lymphoma occurrence.

Malignancy in humans

The data discussed here are compiled from data on drug usage obtained from prescription records and data on adverse events extracted from databases of spontaneous event reports. These data are subject to significant limitations, and while they can serve an important function when used for hypothesis-generating analyses, they cannot reach the conclusions that might be possible when more formal Phase IV studies are performed.

It is important to understand why event rates from data available so far cannot be used to calculate incidence rates that could be compared with national cancer rates. Cancer **incidence** is calculated by dividing the number of events (numerator) by the number of individuals at risk (denominator) and in whom the outcome is able to be detected. **Incidence rates** are calculated by dividing that same numerator by the amount of person-time of exposure to a given risk, again with the caveat that the risk

should be detectable during that person-time. To be valid, the numerator and denominator must be obtained from the same source population studied uniformly. The number of events (numerator) in this situation can be obtained from a self-reported database (AERS - Adverse Event Reporting System) where reporting bias is an issue. Although some clinicians report possible adverse events to the AERS database, many clinicians do not, and their patients cannot properly be included in the denominator of patients at risk of having an event that will be detected. To calculate cancer **incidence** based on these reports, the valid denominator would be the total number of people exposed to the drugs of interest and with the possibility of having a report filed. However, the only denominator available is 'number of filled prescriptions,' which is obtained from an entirely different database and does not describe the population at risk of developing an event and having it reported. To be able to make comparisons with national cancer **incidence rates**, person-time data must be available. The available information regarding the 'number of filled prescriptions' is not person-time data and cannot be used to calculate incidence rates that can validly be compared to national cancer rates.

From 2001 through August 2004, 3.2 million prescriptions have been written for tacrolimus and 18 malignancy-related events have been reported as of November 29, 2004 from AERS (Adverse Event Reporting System). We have tried to obtain more current data from CDER (Center for drug Evaluation and Research) but have not received information at the time of this writing. Of the 18 reported malignancies, 12 were lymphomas and 6 were skin cancers. Person-time follow-up data are not provided (<http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4089b2.htm>) and valid incidence rates cannot be computed and hence cannot be compared with incidence rates from known databases in the US (Surveillance Epidemiology and End Result (SEER) or the Nurses' Health Study (NHS)). The data that are available can also not be used to compute cumulative incidence or other point estimates. One prospective study of 1718 person-years of drug exposure in over 9,000 individuals treated with 0.03% and 0.1% tacrolimus did not find an increased incidence of non-melanoma skin cancer [31].

From 2002 through September 2004, 7.7 million prescriptions were written for pimecrolimus. Since pimecrolimus received marketing approval (12/01), there have been 10 malignancy-related adverse events as of November 29, 2004. The cases included lymphoma (4), 'tumor papilloma (1), basal cell carcinoma (1), squamous cell carcinoma (1), granulomatous lymphadenitis (1), facial tumor (1) and intraductal papilloma of the nipple (1). Although the report presented to the FDA PAC did include a table with age-specific incidence rates for lymphoma, total number of persons or person-time for the post-marketing surveillance data on pimecrolimus (denominator) are not available (<http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4089b2.htm>). Hence, cumulative incidence rates could not be computed.

Other cancers

Single case reports are as follows:

1. Sezary syndrome with tacrolimus after 3 years

2. Hepatoblastoma with tacrolimus after 1 year use
3. Unspecified facial tumor in a child with pimecrolimus (duration unknown)
4. Increase in size of metastatic angiosarcoma with tacrolimus after 3 months.

Post-transplant lymphoproliferative disorder (PTLD) [32, 33] after solid organ or bone marrow transplantation in children is a complication that has been responsible for significant mortality. PTLD's occur in the context of systemic immunosuppression (as is the potential concern with topical TCIs) and infection with Epstein-Barr virus. Early recognition of PTLD and anti-B cell therapies has led to better prognosis. Thus far, there have been no reports in the literature or on AERS on PTLD in patients using tacrolimus or pimecrolimus.

On December 14, 2004, an Office of Drug Safety Post-marketing Safety Review noted that 'spontaneous surveillance systems such as AERS may not be the best tools to determine causality...an active surveillance system such as provided through a registry, may be more useful in determining causality between topical calcineurin inhibitors and malignancy related events. Although, the role of topical calcineurin inhibitors in the development of malignancy related events in the individual reports in our case series is unknown, collectively the AERS cases provide a signal for a possible association between the use of topical calcineurin inhibitors and the development of malignancies.

Phase IV Studies update

When evaluating sporadic reports of adverse events associated with a medication, it is important to understand the reporting mechanisms and their pros and cons [34]. The following disadvantages should be considered when evaluating data from spontaneous reporting system such as the kind the FDA uses to look for early signals. First, cases may be under- or over-reported, depending on patient or physician concern about a particular agent and severity of the adverse event. Second, there is an imprecise understanding of the correlation between adverse event and drug use, which may result in inappropriate reporting and poor report quality. Third, there is absence of denominator data such as total persons or total person-time of follow-up or drug use and summative statistics cannot be calculated. On the other hand, spontaneous reporting systems have some advantages: they are cheaper than formal Phase IV studies, and can be used to survey large populations to generate hypotheses and generate signals of potential problems that need further investigation.

A number of studies have been published on 'safety' of tacrolimus and pimecrolimus. The question readers should be asking is in what context the data published thus far suffice to consider these drugs 'safe'. Phase I, II and III trials address safety to some extent, by documenting acute onset events such as anaphylaxis, irritation, pain or discomfort. Long-term safety evaluation requires Phase IV post-marketing surveillance studies that have a large sample size and extended follow-up. Although there is no precise definition of 'long-term', follow-up of at least 10-15 years may be barely adequate when malignancy is the end-point of concern. The longer the period of follow-up, the better the long-term data are to evaluate potential risk for outcomes such as cancer, which have a long latent period.

A randomized control trial where a population of individuals suffering with AD is randomly assigned to pimecrolimus or tacrolimus or placebo and then followed for the next 20-30 years to evaluate incidence of cancer (lymphoma or skin cancer) is not practical, both due to economic and logistic constraints. The closest next step to better understand long-term safety of the topical calcineurin inhibitors is to collect post-marketing surveillance data in as complete a fashion as possible in patients who are on therapy with these agents as part of their medical care. The FDA has suggested in a report dated January 11, 2005 that 'regulatory action is needed at this time since a definitive answer to the carcinogenic risk of these products will not be known for years and the difficulty of designing a clinical study that will provide a definitive answer to this question'. Below is a discussion of studies designed to respond to this concern. These studies have been implemented at least 3-4 years after approval, delay that has resulted in lost time and data that could have been captured thus far. Pharmaceutical companies have noted that administrative delays in getting these studies approved by the FDA also contribute to the difficulty in initiating the studies whereas the FDA notes that such delays can occur due to their concerns about study design and other related issues. Instead of having the desired Phase IV data, the FDA has to rely on sporadic reports of malignancies that may or may not be related to drug use due to the problematic nature of such reporting, as discussed

above. From the perspective of the clinician and individual with AD, to-date no Phase IV data has been reported on or is otherwise available for analysis and comment for tacrolimus or pimecrolimus.

PEER (Pediatric Eczema Elective Registry), Novartis.

As part of the Phase IV commitment, Novartis agreed to conduct a long-term prospective observational study in children. PEER is a parent-reported epidemiologic registry and enrollment is through local physicians; no tests, exams or medical intervention is required. Parents complete a survey at enrollment and every six months for 10 years. Age limits are 2-17 years. Participants must have used pimecrolimus for six weeks (42 days) in the last six months, and this does not have to be continuous use to be eligible. Physicians may be pediatricians, dermatologists, pediatric dermatologists, primary care physicians, or family physicians. Parents receive \$25 for each survey received. The first patient was enrolled in November 2004 and approximately 930 patients have enrolled thus far, based on most recent information available from Novartis at the time of this writing. The website at www.thepeerprogram.org and phone number 877-711-7337 can both be used by parents and physicians. Forms are mailed to physicians. A PEER program is in place to encourage physicians to submit forms, and for parents to be made aware of the registry. The goal is to enroll 4,000 participants by April 2006.

Non-Melanoma Skin Cancer (NMSC) Registry, Novartis.

This study is a retrospective case-control study of 5000 patients selected from a database at one site only (University of Pennsylvania). Investigators will evaluate the number of patients who used topical calcineurin inhibitors.

APPLES (Atopic Prospective Pediatric Longitudinal Evaluation Study), Astellas.

As part of the Phase IV commitment, Fujisawa (now Astellas) agreed to conduct a long-term prospective observational study in individuals treated with tacrolimus. This study is designed to assess long-term safety of tacrolimus ointment for the treatment of AD. It is a multinational, observational cohort study of 8,000 patients followed for 10 years. About 6,500 of these will be recruited from the US. There will be direct patient contact every six months by phone or mail survey, an annual physical examination, biannual dermatologic exam will be performed and subjects will be followed regardless of tacrolimus ointment use during the study. The study is powered to detect three-fold increased risk in cutaneous/systemic malignancies. For inclusion in the study, participants must be under age 16 years at first exposure and be treated with 0.03% or 0.1% tacrolimus ointment for at least six weeks, continuously or intermittently. Study end-points include systemic malignancies (Hodgkin's disease, Non-Hodgkin's lymphoma) and skin cancer (melanoma and non-melanoma skin cancer). The first patient was recruited in May 2005 and a total of about 70 participants have been recruited at the time of this writing based on information available from Astellas. The study phone number is 877-277-7530. Attention has been paid to study design, selection of a valid cohort and cohort retention over the term of the study.

Prescribing and drug usage

One of the major concerns about topical calcineurin inhibitors has been aggressive promotional campaigns and advertising that have resulted in increased prescribing of these agents, especially for children < 2 years age. In a report dated January 11, 2005, the FDA commented on “aggressive and inappropriate advertising with portrayal of these agents as safer than steroids and the implication that they can be used as first-line therapy and for unlimited periods of time.”

In Postmarketing Safety Reviews from the Office of Drug Safety (ODS) dated September 28, 2004 for pimecrolimus and October 5, 2004 for tacrolimus the following was noted about change in prescribing for each medication:

1. Pimecrolimus – About 13% of all pimecrolimus was used in children <age 2 years and number of prescriptions increased more than 2-fold from 2002 (>1.5 million) to 2003 (>3.4 million).
2. Tacrolimus – About 7% of all tacrolimus was used in children < age 2 years and number of prescriptions increased from 2001 (>0.6 million) to 2003 (>0.9 million).

First-line therapy

Tacrolimus and pimecrolimus are being used as first-line agents in several clinical settings such as on the face in adults and on the body in children. The FDA has expressed concern that these drugs were not initially approved for use as first-line agents and that topical steroids are the mainstay of topical therapy in atopic dermatitis. Physicians have traditionally retained the prerogative to prescribe drugs off-label, generally in circumstances that were not directly studied in pre-approval research trials. One concern for the FDA is that the extremely high prescribing rates of the topical calcineurin inhibitors exceed the rate that might reasonably be expected as ‘off-label’ use for new medications and suggests that many clinicians have simply adopted these drugs as first-line agents.

Continuous therapy to prevent disease worsening

Tacrolimus and pimecrolimus have an advantage over topical steroids because they do not cause atrophy, erythema, striae and pigmentation changes. However, the long-term effects of both drugs on the skin as well as systemically are unknown at this time. The FDA is concerned that both drugs have been marketed aggressively based on reduced short-term skin-specific side effects, resulting in long-term use of the medications on larger areas of the body which may result in greater systemic absorption and longer-term effects on the skin such as promotion of skin cancers.

Use in children < 2 years age

Tacrolimus and pimecrolimus are not indicated in children < age 2 years. As above, due to the short-term favorable skin-related adverse effect of both tacrolimus and pimecrolimus as compared to topical steroids, the FDA is concerned that the drugs are being inappropriately marketed to pediatricians and non-dermatologists who may be otherwise hesitant to use a topical steroid. Data so far suggest that a significant

number of prescriptions are being written for both tacrolimus and pimecrolimus for children in this age group, despite this being off-label use of the drugs.

The ‘black box’ warning

The Division of Pediatric Drug Development (DPDD), Pediatric Advisory Committee (PAC) of the Food and Drug Administration (FDA) has discussed a boxed warning for tacrolimus (Protopic®) and pimecrolimus (Elidel®). The reasons for suggestion of such action are:

1. reports of lymphoma and skin cancer in some individuals using these topical calcineurin inhibitors from post-marketing surveillance data, and
2. concerns about systemic absorption resulting in greater systemic exposure in a sub-population of treated patients
3. unusually aggressive and inappropriate marketing of topical calcineurin inhibitors as first-line agents
4. early carcinogenicity signal in animals treated with very high systemic doses of these agents

There are a number of examples of other medications such as droperidol [35, 36] or pediatric antidepressants [37, 38], where the black box warning has been much debated in the literature. In 1979, the FDA issued regulations on the format and content of prescription drug labeling in the United States. These regulations covered the Description, Clinical Pharmacology, Indications and Usage, Contraindications, Warnings, Precautions, Overdosage, Dosage and Administration, and How Supplied that are seen in the Physicians’ Desk Reference as well as prescription drug package inserts. In the Warnings section the regulations note that: Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data.

This section of the regulations is the primary regulatory source that empowers the FDA’s use of the black box warning. Apart from package inserts and Physicians’ Desk Reference materials that are the subject to the black box warning, all labeling is subject to the rule, including brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, letters, exhibits, literature, reprints, as well as any other materials in audio, visual, or print matter form that describe the use of the drug by medical practitioners, pharmacists, or nurses. Moreover, FDA regulations do not allow for the drug manufacturer to issue unilaterally a black box warning for its drug; it may only do so when required by the FDA. Use of a black box warning is usually limited to “the most serious warnings necessary to ensure the continued safe use of the product.”

Evidence summary

1. Topical pimecrolimus and tacrolimus are two new topical calcineurin inhibitors that can be used for the treatment of atopic dermatitis
2. Their advantage over topical steroids is that they do not cause skin thinning or ocular side effects, making them especially useful for sites such as the face where skin thinning may develop quickly
3. Short-term data on systemic side effects for tacrolimus and pimecrolimus are reassuring, systemic absorption is low in majority of patients, and cancer takes years to develop; long-term safety data are incomplete
4. Both agents have been used “off-label” extensively i.e. in those under 2 years, and both agents have been portrayed as being safe for long term use during marketing
5. Recent concerns triggered by sporadic spontaneous case report of skin cancers in adults and lymphomas in children have caused the FDA to consider a “black box” warning for both these agents
6. Sporadic case reports are an unreliable source to infer causation – at best they can serve as a signal for a possible association; long-term data from Phase IV studies is not available and 4-5 years of potential data have been lost because these studies were not initiated promptly
7. Animal studies suggest that when used at very high systemic doses, both agents may be associated with the development of skin cancers and lymphomas
8. Phase IV post-marketing surveillance studies are probably the best form of data to answer the question on whether topical tacrolimus and pimecrolimus may cause cancer
9. Two such comprehensive studies have just recently been set up by pharmaceutical companies who manufacture topical tacrolimus and pimecrolimus
10. It will take another 5 to 10 years before enough data is available from such studies to help understand a possible association, if any, between topical tacrolimus and pimecrolimus use and cancer occurrence
11. The possible association between topical tacrolimus and pimecrolimus and cancer therefore remains unclear and physicians have been urged by the FDA to only use these agents within strict indications in order to maximize benefits for those who need it and to limit unnecessary use.
12. Physicians and patients need to work closely together to ensure clinical follow-up and compliance with therapy.

Authors' opinion and interpretation

The development of topical calcineurin inhibitors is an advance in the management of atopic dermatitis because of their lack of skin thinning potential. The availability of these agents for topical use fills a therapeutic void for the patient living day-to-day with life-altering AD that has a major impact on quality of life. On the other hand, the original clinical trial data do not suggest a significant efficacy advantage for the topical calcineurin inhibitors as compared to topical steroids, and there is not yet adequate evidence to support topical calcineurin inhibitors as first-line therapy for AD. Aggressive marketing of the topical calcineurin inhibitors by their manufacturers has led to wide-spread adoption of these agents by prescribers, including notable trends toward first-line prescribing and off-label use.

There is also the safety concern raised by sporadic reports of malignancy of the skin and lymphoma, combined with prior research demonstrating that a small percentage of patients treated with topical calcineurin inhibitors have significant systemic absorption of the agent. These reports constitute a possible signal that requires further investigation. At this stage, however, definitive data are not available to make conclusions about any causal association between these two drugs and malignancy. On the other hand, it would be irresponsible to declare both drugs completely safe in the atopic dermatitis patient. The best way to investigate this association is with Phase IV studies; indeed such studies were requested by the FDA when the drugs were approved and were agreed to by the manufacturers at that time. Unfortunately, the Phase IV studies have only just begun to enroll patients, and many years are likely to pass before conclusive safety data are available.

The FDA is considering imposing a black box warning for both drugs. Over-marketing by the companies, coupled with delay in initiation of mandated Phase IV studies has brought the FDA to this stage. It is unfortunate that the FDA sees the black box warning as the only policy-related method to enforce regulatory commitments and restrict aggressive marketing efforts. Concerned clinicians and organizations such as NEASE should step in and work towards the optimal clinical outcome: educating providers about the need for cautious and limited prescribing of topical calcineurin inhibitors in the appropriate clinical setting, careful monitoring and follow-up of AD patients receiving therapy, advocating for definitive studies to be done, and facilitating forward movement for such studies e.g. helping recruit AD patients into such studies. Atopic dermatitis patients would be best served by rigorously run Phase IV studies, better informed prescribers, restricted marketing and use of both drugs, and intermittent evaluation of data collected to detect the earliest possibly harmful signal.

Guidance for individuals with atopic dermatitis and their providers

Organizations such as NEASE, the FDA, scientists and clinicians across the country and the companies that make tacrolimus and pimecrolimus are all trying to provide information on the safety and efficacy of these drugs. The overall message may be confusing to individuals suffering with atopic dermatitis and their physicians or other providers. This report is a step forward in better understanding the issue of tacrolimus and pimecrolimus safety in the context of cancer occurrence. The message this report provides is as follows:

There is concern that tacrolimus and pimecrolimus may be associated with cancer occurrence. These drugs have not been proven to be completely safe at this point in time, but formal research studies to determine their safety have now been initiated. It will take at least 5-10 years before we have more information. Until then, the drugs should continue to be used in certain cases as an alternative to or in combination with topical steroids, but use should be carefully monitored and patients followed closely. Efficacy compared to topical steroids should help guide physicians to pick the drug most appropriate for their patients. Among children, their use should be restricted to those older than 2 years age. For physicians, there is no better guidance than judicious clinical judgment. For those suffering with atopic dermatitis, there is no better substitute than good compliance with the therapeutic plan and follow-up with their physician.

References

1. Sicherer, S.H. and D.Y. Leung, *Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects*. Journal of Allergy & Clinical Immunology, 2005. **116**(1): p. 153-63.
2. Stander, S. and M. Steinhoff, *Pathophysiology of pruritus in atopic dermatitis: an overview*. Experimental Dermatology, 2002. **11**(1): p. 12-24.
3. Spergel, J.M. and A.S. Paller, *Atopic dermatitis and the atopic march*. Journal of Allergy & Clinical Immunology, 2003. **112**(6 Suppl): p. S118-27.
4. Leung, D.Y., et al., *New insights into atopic dermatitis*. Journal of Clinical Investigation, 2004. **113**(5): p. 651-7.
5. Ellis, C.N., et al., *Cost of atopic dermatitis and eczema in the United States*. Journal of the American Academy of Dermatology, 2002. **46**(3): p. 361-70.
6. Cono, J., et al., *Smallpox vaccination and adverse reactions. Guidance for clinicians*. Morbidity & Mortality Weekly Report. Recommendations & Reports, 2003. **52**(RR-4): p. 1-28.
7. Wittkowski, A., et al., *The impact of psychological and clinical factors on quality of life in individuals with atopic dermatitis*. Journal of Psychosomatic Research, 2004. **57**(2): p. 195-200.
8. Evers, A.W., et al., *Common burden of chronic skin diseases? Contributors to psychological distress in adults with psoriasis and atopic dermatitis*. British Journal of Dermatology, 2005. **152**(6): p. 1275-81.
9. Grob, J.J., et al., *Comparative study of the impact of chronic urticaria, psoriasis and atopic dermatitis on the quality of life*. British Journal of Dermatology, 2005. **152**(2): p. 289-95.
10. Holm, E.A. and G.B. Jemec, *Time spent on treatment of atopic dermatitis: a new method of measuring pediatric morbidity?* Pediatric Dermatology, 2004. **21**(6): p. 623-7.
11. McKenna, S.P., et al., *International development of the Parents' Index of Quality of Life in Atopic Dermatitis (PIQoL-AD)*. Quality of Life Research, 2005. **14**(1): p. 231-41.
12. Carroll, C.L., et al., *The burden of atopic dermatitis: impact on the patient, family, and society*. Pediatric Dermatology, 2005. **22**(3): p. 192-9.
13. Arima, M., et al., *Psychosomatic analysis of atopic dermatitis using a psychological test*. Journal of Dermatology, 2005. **32**(3): p. 160-8.
14. Chamlin, S.L., et al., *Effects of atopic dermatitis on young American children and their families*. Pediatrics, 2004. **114**(3): p. 607-11.
15. Qureshi, A.A., et al., *Report on "Burden of Skin Disease" Workshop. NIAMS, September 2002*. Journal of Investigative Dermatology. Symposium Proceedings, 2004. **9**(2): p. 111-9.
16. Housman, T.S., et al., *Tacrolimus ointment: utilization patterns in children under age 2 years*. Dermatology Online Journal, 2004. **10**(1): p. 2.
17. Siklar, Z., et al., *An infantile Cushing syndrome due to misuse of topical steroid*. Pediatric Dermatology, 2004. **21**(5): p. 561-3.

18. Woo, W.K. and K.E. McKenna, *Iatrogenic adrenal gland suppression from use of a potent topical steroid*. *Clinical & Experimental Dermatology*, 2003. **28**(6): p. 672-3.
19. Matsuda, K., et al., *Adrenocortical function in patients with severe atopic dermatitis.[see comment]*. *Annals of Allergy, Asthma, & Immunology*, 2000. **85**(1): p. 35-9.
20. Simpson, D. and S. Noble, *Tacrolimus ointment: a review of its use in atopic dermatitis and its clinical potential in other inflammatory skin conditions*. *Drugs*, 2005. **65**(6): p. 827-58.
21. Ashcroft, D.M., et al., *Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials.[see comment]*. *BMJ*, 2005. **330**(7490): p. 516.
22. Reitamo, S., et al., *A multicentre, randomized, double-blind, controlled study of long-term treatment with 0.1% tacrolimus ointment in adults with moderate to severe atopic dermatitis*. *British Journal of Dermatology*, 2005. **152**(6): p. 1282-9.
23. Garden, J.M. and R.K. Freinkel, *Systemic absorption of topical steroids. Metabolic effects as an index of mild hypercortisolism*. *Archives of Dermatology*, 1986. **122**(9): p. 1007-10.
24. Barnetson, R.S. and A.D. White, *The use of corticosteroids in dermatological practice*. *Medical Journal of Australia*, 1992. **156**(6): p. 428-31.
25. Billich, A., et al., *Percutaneous absorption of drugs used in atopic eczema: pimecrolimus permeates less through skin than corticosteroids and tacrolimus*. *International Journal of Pharmaceutics*, 2004. **269**(1): p. 29-35.
26. Staatz, C.E. and S.E. Tett, *Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation*. *Clinical Pharmacokinetics*, 2004. **43**(10): p. 623-53.
27. Nghiem, P., G. Pearson, and R.G. Langley, *Tacrolimus and pimecrolimus: from clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis*. *Journal of the American Academy of Dermatology*, 2002. **46**(2): p. 228-41.
28. Soter, N.A., et al., *Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part II, safety*. *Journal of the American Academy of Dermatology*, 2001. **44**(1 Suppl): p. S39-46.
29. Paller, A., et al., *A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in pediatric patients*. *Journal of the American Academy of Dermatology*, 2001. **44**(1 Suppl): p. S47-57.
30. Kawashima, M., et al., *Tacrolimus concentrations in blood during topical treatment of atopic dermatitis*. *Lancet*, 1996. **348**(9036): p. 1240-1.
31. Naylor, M., et al., *Non-melanoma skin cancer in patients with atopic dermatitis treated with topical tacrolimus*. *Journal of Dermatological Treatment*, 2005. **16**(3): p. 149-53.
32. Faye, A. and E. Vilmer, *Post-transplant lymphoproliferative disorder in children: incidence, prognosis, and treatment options*. *Paediatric Drugs*, 2005. **7**(1): p. 55-65.
33. Ghobrial, I.M., et al., *Prognostic factors in patients with post-transplant lymphoproliferative disorders (PTLD) in the rituximab era*. *Leukemia & Lymphoma*, 2005. **46**(2): p. 191-6.

34. Hauben, M., *A brief primer on automated signal detection*. *Annals of Pharmacotherapy*, 2003. **37**(7-8): p. 1117-23.
35. Dershwitz, M., *There should be a threshold dose for the FDA black-box warning on droperidol.[comment]*. *Anesthesia & Analgesia*, 2003. **97**(5): p. 1542-3; author reply 1543.
36. Gan, T.J., *"Black box" warning on droperidol: report of the FDA convened expert panel*. *Anesthesia & Analgesia*, 2004. **98**(6): p. 1809.
37. Kondro, W., *FDA urges "black box" warning on pediatric antidepressants*. *CMAJ Canadian Medical Association Journal*, 2004. **171**(8): p. 837-8.
38. Licinio, J. and M.L. Wong, *Depression, antidepressants and suicidality: a critical appraisal*. *Nature Reviews. Drug Discovery*, 2005. **4**(2): p. 165-71.