

The Frequency and Intensity of Topical Pimecrolimus Treatment in Children with Physician-Confirmed Mild to Moderate Atopic Dermatitis

Roger Kapoor, M.D., M.B.A.,* Ole Hoffstad, M.A.,† Warren Bilker, Ph.D.,†
and David J. Margolis, M.D., Ph.D.†‡

**Department of Dermatology, Massachusetts General Hospital, Harvard University School of Medicine, Boston, Massachusetts, †Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, ‡Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania*

Abstract: Atopic dermatitis (AD) is often treated with multiple modalities, including topical medications such as corticosteroids and topical calcineurin inhibitors (TCIs). The aim of this study was to describe the natural history of the utilization characteristics of topical treatment in those with AD. We conducted a longitudinal study of the first 4,105 children with physician-confirmed mild to moderate AD enrolled in an ongoing postmarketing safety study of pimecrolimus. Information was obtained from participants every six months using a questionnaire. Drug utilization was solely determined by the physician and patient. Over the three years of our study, an increasing number of individuals reported at least 6 months of complete control of their disease, without the continued use of a topical medication. While all study participants used pimecrolimus at the start of the study less than 40% continued to use it after 3 years of study participation. If an individual was still using a topical medication after three years of follow-up, it was most likely a topical corticosteroid. For those who continued to use pimecrolimus, the use was limited to about 60 grams of pimecrolimus in 6 months. Community-based use of topical pimecrolimus to treat AD is limited both with respect to the duration of exposure and amount or total dose of the exposure. If a topical therapy is persistent, it is most likely to a topical corticosteroid.

Atopic dermatitis (AD) or eczema is a very common ailment manifested by pruritic erythematous patches that most frequently occur in the flexural areas of the elbows and knees (1,2). The lifetime prevalence of AD is about

5% to 20%, with nearly all reporting skin problems when they were less than 18 years of age (2,3). As many as 40% of patients with AD prior to the third year of life will have disease that persists at least 6 years, but by age 10, 60%

Address correspondence to Roger Kapoor, M.D., M.B.A., 55 Fruit Street, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114.

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to 70% will be free of symptoms (2,4). A recent worldwide study has shown that in almost all parts of the world there is an increase in the prevalence of eczema with the prevalence increasing by about 0.25% per year. The total estimated annual cost in the United States in 2004 due to AD was estimated to be about \$1.6 billion with an additional billion dollars believed to represent the diminished quality of life associated with AD (patients and parents) (5). These figures do not include the costs and burdens due to asthma, seasonal allergies, or other atopic diatheses, the onset of which frequently occur after the onset of AD and are associated with AD. AD clearly causes a major financial burden to both individual families and national health care systems.

Patients with AD are often treated with multiple modalities that often include topical medications. While side effects due to both the acute and chronic use of topical medications have been reported and hypothesized, very little has been published about the long-term frequency or intensity of topical drug use in AD patients. Understanding how topical medications are used in this population over the course of childhood is important for several reasons including understanding the potential safety risks that could be associated with long-term chronic use of topical medications. The Pediatric Eczema Elective Registry (PEER; <http://www.thepeerprogram.org>) is an ongoing prospective 10-year observational registry that is part of a postmarketing commitment by Novartis to the Food and Drug Administration (FDA) and the European Medicines Agency. The individuals in this registry represent a unique opportunity to evaluate the natural history of AD topical medication use in a group of children with a physician-confirmed diagnosis of AD. The primary goal of this study was to describe the frequency and intensity of topical treatment in those with AD enrolled in the PEER study.

METHODS

Study Design and Population

All subjects were part of an ongoing 10-year prospective observational cohort study (registry), called PEER, of children with mild to moderate AD, who were exposed to pimecrolimus cream (6). For our study 4,105 consecutively enrolled children in our ongoing postmarketing study between the ages of 2 and 17 years at the time of consent were evaluated. Enrollment was nationwide (USA) through the physician's office (dermatologists, pediatric dermatologists, pediatricians, allergists, other treating physicians, or combinations of these). All subjects had a physician's clinical diagnosis of AD. All individuals enrolled in

this registry had a total of at least 6 weeks of exposure to pimecrolimus cream. The exposure had to be either six continuous weeks or six total weeks of intermittent exposure within 6 months prior to enrollment. Once enrolled in the study, exposure to pimecrolimus or another medication is determined by the treating physician alone and is not dependent on a study protocol. Study participants received survey questionnaires at the time of enrollment, and then at 6 month intervals (i.e., 6, 12, 18, 24, 30, and 36 mos). It is important to note that the primary goal of the PEER study is to evaluate whether topical pimecrolimus use is associated with systemic and cutaneous malignancies and that this study is ongoing and subjects are still actively being enrolled. As a result, varying numbers of subjects have reached each study survey time point. Although subjects are directed to answer all questions, not all study subjects who returned a survey answered every question. Due to the subject's age, in most cases the questionnaires were completed by their parents or caregivers in most cases. The PEER questionnaire was created to survey the epidemiologic and clinical characteristics of AD in the U.S. pediatric population. Many of our questions were modeled after the International Study of Asthma and Allergies in Childhood (ISAAC) study. Individuals with a history of lymphoproliferative disease or who used systemic immunosuppression medications (i.e., cyclosporine, tacrolimus, and methotrexate) were excluded from the study. The goal of the current analysis is a secondary aim to describe the patterns of use of topical therapies for those with AD. This study was approved by the Institutional Review Board of the University of Pennsylvania.

Definitions of Variables

Topical pimecrolimus, tacrolimus, and corticosteroid usage was determined at each survey interval by asking subjects whether they had used these products in the preceding 6 months. The amount of medication used was determined by asking for the tube size and number of tubes used in the previous 6 months. Total pimecrolimus cream 1% with or without tacrolimus ointment use in grams was calculated for each 6 month survey interval. Subjects, or their caregivers, were also asked to report on the use of topical corticosteroids during the same time interval.

Subjects, or their caregivers, were asked to rate their level of disease control according to the following categories: complete control, good disease control, limited disease control, and uncontrolled disease. The total time an individual had AD, in years, was calculated from their

reported first diagnosis of AD to the time of our analyses. Age categories were based on the subject's age upon entry date into the PEER cohort.

Method of Analysis

For this longitudinal study, we used descriptive statistics to calculate simple percentages or means and standard deviation (SD). Chi-squared or logistic regression was used to evaluate the association of age and age of onset with the likelihood of not using topical medications as well as changes in drug use overtime. Statistical analysis was conducted using Stata, Version 9.2 (Stata Corp, College Station, TX). It is important to note that due to the large size of our study small clinically unimportant differences in utilization could result in very small statistically significant p-values after statistical testing. For that reason we also report odds ratios in order to better illustrate our findings.

RESULTS

We analyzed data from 4,105 pediatric subjects entered in the PEER study. Surveys on these individuals were carried out every 6 months after their enrollment. Enrollment has been ongoing since November 2004, so, for the purposes of this analysis, some patients may have been followed for less than 6 months while others for as long as 36 months. In the time period of the present

analysis, 2,530 individuals were followed for at least 1 year, 1,533 for at least 2 years, and 516 for at least 3 years. In our sample 46.3% were males, 53.7% females, and 58% were from a minority group. The mean age at enrollment was 7.1 years (SD $\pm$ 4.0) with a median of 6.1 years. The average age of onset for AD was 2.2 years ($\pm$ 2.9 SD). The median age of onset was 0.8 years (25th percentile 0.3, 75th percentile 3.0). During the time interval of this analysis, and based on self-reporting, patients had AD for a mean of 4.9 years (SD $\pm$ 3.6) and median of 3.9 years of AD. Approximately 48% of participants thought that their AD was poorly controlled in the 6 months prior to enrollment and about 32% had signs of AD in three or more body sites (e.g., elbow creases, knee creases, face, buttocks, abdomen, etc.).

All subjects on entry into the study had already been exposed to pimecrolimus cream. However, by 6 months 12.8%, by 12 months 22.6%, by 18 months 29.1%, by 24 months 34%, by 30 months 36.4%, and by 36 months 45.4% were no longer using pimecrolimus cream (Table 1, $p < 0.0001$; OR and 95% CI: 1.66: [1.62, 1.70]). On enrollment into our study about 15.8% of subjects had also used tacrolimus ointment. Topical tacrolimus use declined at a rate similar to topical pimecrolimus use, such that by the 36th month only 4.3% of subjects were still using tacrolimus ointment. About 43.7% of subjects had not used corticosteroids at enrollment. Compared to the topical calcineurin inhibitors (TCI), the use of corticosteroids varied less

TABLE 1. *Percentage of Subjects Reporting No Use of Pimecrolimus, Topical Corticosteroids, or Topical Drugs Over Time*

Compound	Enroll	0–6 mos	Year 1	12–18 mos	Year 2	24–30 mos	Year 3
Percentage of subjects no longer using pimecrolimus	0 (0/4,105)	12.8 (363/2,829)	22.6 (571/2,525)	29.1 (590/2,026)	34.0 (521/1,532)	36.4 (439/1,207)	45.4 (234/516)
Percentage of subjects no longer using corticosteroids	43.7 (1,792/4,103)	52.5 (1,487/2,826)	51.5 (1,225/2,529)	50.1 (1,017/2,025)	50.7 (778/1,530)	50.5 (610/1,206)	49.0 (253/516)
Percentage of subjects no longer using topical medications	0 (0/4,105)	4.2 (118/2,829)	6.9 (176/2,530)	9.9 (201/2,027)	12.5 (192/1,533)	14.7 (178/1,207)	15.5 (80/516)

The number of subjects reporting no use (numerator) and the total number of subjects who responded to the question (denominator) for each cell are listed in parentheses.

TABLE 2. *Percentage of Subjects who Stopped Using Topical Medications as Noted in the Treatment Column*

Treatment	Enroll (4,105)	0–6 mos (2,829)	Year 1 (2,530)	12–18 mos (2,027)	Year 2 (1,533)	24–30 mos (1,207)	Year 3 (516)
No topical treatment	0 (0/4,105)	4.2 (118/2,829)	6.9 (176/2,530)	9.9 (201/2,027)	12.5 (192/1,533)	14.7 (178/1,207)	15.5 (80/516)
No pimecrolimus use among solo users	0 (0)	11.5 (122/1,057)	19.5 (177/908)	25.4 (190/749)	32.4 (189/584)	35.1 (156/444)	43.0 (77/179)
No pimecrolimus use among those originally on pimecrolimus and corticosteroids	0 (0)	13.2 (216/1,638)	24.0 (355/1,480)	30.8 (359/1,165)	34.4 (303/881)	36.7 (264/719)	45.3 (144/318)
No drug use among those originally on pimecrolimus and corticosteroids	0 (0)	3.8 (63/1,638)	8.0 (118/1,483)	10.4 (121/1,166)	11.6 (102/881)	15.6 (112/719)	14.5 (46/318)

The number of subjects reporting no use (numerator) and the total number of subjects who responded to the question (denominator) for each cell are listed in parentheses.

over time than did use of the TCI ($p < 0.001$, 1.05 [1.03, 1.07]). By 6 months 4.2%, by 12 months 6.9%, by 18 months 9.9%, by 24 months 12.5%, by 30 months 14.7%, and by 36 months 15.5% claimed to have stopped using all topical medications ($p < 0.0001$, 1.65 [1.62, 1.70]). The majority of those that stopped all medications had enrolled in the study as solo users of pimecrolimus cream (e.g., by year 2, 32.4% vs 1.6%; Table 2). Interestingly, a similar percentage of individuals stopped using pimecrolimus who originally enrolled as users of both pimecrolimus and corticosteroids as those who enrolled as pimecrolimus users alone (e.g., by year 2, 34.4% vs 32.4%, 43% vs 45.3%). In other words, over time if an individual in our cohort continued to use a topical medication to treat their AD it was most likely a corticosteroid. A similar trend was noted with respect to the total quantity of pimecrolimus cream used. Over time the mean and median reported 6 month use of pimecrolimus cream for the group decreased from 100 g to 30 g. With respect to the use of pimecrolimus cream among those who claimed to still be pimecrolimus users, their overall grams of use also decreased at each survey period. The median 6 month use of pimecrolimus was 100 g on entry into the study and 30 g by the third year of participation for those who still used pimecrolimus. The changing pattern of topical medication use did not depend on the age of the subject on entry into our study or on the length of time they had been afflicted with AD on entry into the study ($p = 0.3$).

The percentage of subjects who claimed at least good control of their disease increased progressively from 52.0% at the start of the study to 72.4% by the end of the third year of our study. The percentage who claimed to be under complete control increased progressively from 4.5% at enrollment to 16.0% by the third year of observation. Finally, 4.1% by month 6, 4.9% by month 12, 6.1% by month 18, 7.6% by month 24, 7.5% by month 30, and 8.9% by month 36 claimed to have had at least 6 months of complete control of their disease and claimed to have stopped using all topical medication.

DISCUSSION

Unique conclusions regarding the persistence of mild to moderate AD enrolled in the PEER study as well as the natural history of topical drug use for the treatment of AD can be made. We describe an increasing number of individuals who report either complete or at least good disease control of their AD by the end of the third year of the study as compared to the start of the study. In fact, about 15% of the individuals reported at least 6 months of complete disease control, without the continued use of

a topical medication. Even though required for study eligibility the use of pimecrolimus cream was not consistent and over time, those still using a topical medication were most likely using a corticosteroid. Indeed, at 12 months, approximately one-third of the patients were no longer using pimecrolimus cream; at 36 months, this number had increased to 50%. For those still using pimecrolimus cream, a smaller quantity of pimecrolimus was used (i.e., the vast majority used ≤ 1 tube, limited to approximately 60 g). Overall our findings were not influenced by age.

The TCI, namely pimecrolimus and tacrolimus, became available as topical formulations for the treatment of AD about 7 years ago (7–9). They are currently indicated as second-line agents in the treatment of AD (e.g., for patients who have not responded to other topicals) (10). In 2005 the FDA noted a lack of knowledge about the long-term safety of TCI and cautioned about the possible association of TCI use and malignancy (11). This “black boxed” warning cautioned against continuous long-term use and the application of these agents in areas affected by AD (12). This concern stems partly from previous documentation of an increased frequency of skin cancer and Epstein–Barr virus-associated lymphoma associated with the use of oral calcineurin inhibitors, especially in patients with organ transplants after early high dose or prolonged exposure (13,14). Similarly, an increased risk of lymphoma was generally seen only after long-term high level exposure to TCI in animals (15). In humans, the potential for TCI to cause skin cancer is much less clear (16). Given these findings and our demonstration of how TCI are used in the general population, there may be less of a reason to worry about the potential effects of TCI exposure in most patients, as described in the black boxed warnings.

Several possible explanations for patients discontinuing pimecrolimus exist, including the influence of the FDA black boxed warning, the cost of pimecrolimus versus corticosteroids, effectiveness of corticosteroids, or the subject’s current severity and natural history of mild to moderate AD. Less than 1% of our subjects enrolled before the FDA issued a boxed warning, so it is difficult to arrive at firm conclusions on the effect the black box warning had on the use of pimecrolimus cream in our study. In addition, several studies have been published showing that black boxed warnings in general do not have a major impact on how a drug is used (17,18).

Several characteristics of this study enhance the validity of our findings. In the past, definitions for AD in large observational studies have been inconsistent (19–21). All study subjects in this study had a physician-confirmed diagnosis of AD, and had a minimum of 6 weeks of exposure to pimecrolimus cream. We believe

this criterion allows for confident conclusions to be drawn regarding our relatively homogenous cohort of children given a diagnosis of AD by a physician. As we did not study those who were not determined to have AD by a physician, our results do not generalize to all individuals who may receive a TCI for dermatitis. Our population is also geographically, demographically, and economically diverse (6).

As with all studies, there are design limitations to consider. While the diagnosis of AD was confirmed by a physician, a parent or primary caregiver (or patient after age 18 yrs) reports all other data. The basis for these reports is the ISAAC survey questions and, therefore, our results can be compared with a large, diverse amount of published literature (3,22). Participation in our study is voluntary and this may play a role in the results observed in the form of a recall bias. Our information on topical exposure to TCI and corticosteroids is based on the patient's (or caregiver's) self-reporting. This type of reporting can affect the accuracy of our ability to measure TCI use. We did not collect information on the potency of the topical steroid in use, so while we do know that participants continue to use topical corticosteroids we do not know whether they are using less potent or more potent ones over time.

In summary, our current report is the largest longitudinal evaluation of children with a diagnosis of AD in the United States. We found that for a large number of individuals with mild to moderate AD, skin complaints are not persistent and their topical drug use for AD markedly decreases over time. This decrease in use is most dramatic for TCI. For those still using a TCI, our findings suggest that an individual's quantity of exposure decreases with time (≤ 1 tube). If a topical medication is continued, it is most likely a topical corticosteroid. Based on the findings from this observational study on TCI usage and the wide safety margin that exists between blood levels that are associated with the risk of malignancy and those found in patients using pimecrolimus cream 1%, it is very unlikely that an individual using TCI, as part of community-based care, could be exposed to the intensity or duration of calcineurin inhibition seen in solid organ transplant patients using oral calcineurin inhibitors who are at risk of developing a malignancy.

CONFLICTS OF INTEREST DISCLOSURE

David Margolis has a consulting relationship with Astellas Pharmaceuticals. All of the other authors do not have consulting relationships or financial interests that could be perceived as a conflict of interest. All authors had full access to all of the data in the study and take

responsibility for the integrity of the data and accuracy of the data analysis. All authors were involved in the study concept and design, the acquisition of the data, the analysis and interpretation of the data, as well as the drafting and critical revision of the manuscript.

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