Formulary Review of Therapeutic Alternatives for Atopic Dermatitis: Focus on Pimecrolimus

JEFFREY M. WEINBERG, MD

ABSTRACT

OBJECTIVE: Atopic dermatitis (AD), often called eczema, is characterized by intense pruritus, erythema, dry skin, and inflammation. The condition is chronic and relapsing, and often occurs in patients with a family history of the atopic triad (asthma, allergic rhinitis, and AD). Use of topical steroids has been the mainstay of medical treatment for AD. Steroid-free treatments for AD, with a more favorable safety profile, have become available within the past 2 years. Tacrolimus ointment, a topical immunomodulator, became available in early 2001 and is indicated for moderate-to-severe AD. A similar but highly skin-selective cytokine inhibitor, pimecrolimus cream 1%, became available in March 2002. Pimecrolimus is indicated for mild-to-moderate AD. The objective of this article is to review the key characteristics that differentiate pimecrolimus from steroids and tacrolimus in the treatment of AD.

METHODS: Using secondary resources, the clinical aspects and conventional treatment strategies for AD are reviewed as are the pivotal clinical studies with pimecrolimus and literature on quality of life and economic burden of disease for AD patients and families.

SUMMARY: Pimecrolimus is an effective, steroid-sparing therapy for mild-to-moderate AD. Early treatment prevents flares, the agent works quickly to reduce signs and symptoms of more advanced AD, and it is safe and appropriate for intermittent long-term therapy. Pimecrolimus has fewer side effects than topical steroids and a better side-effect profile than tacrolimus. It can also be used as a first-line therapy. In studies with patients aged 2 to 17 years, it has been shown to be particularly effective in improving eczema of the face and neck, and its use may improve quality of life for many patients, especially children. A single-strength dose (1%) is safe and medically beneficial for pediatric, adolescent, and adult patients. The direct drug cost of pimecrolimus compares favorably with tacrolimus, but it is significantly more expensive than generic topical steroid creams.

KEYWORDS: Atopic dermatitis, Nonsteroid, Cytokine inhibitor, Topical immunomodulator

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Atopic dermatitis (AD), often called eczema, is characterized by intense pruritus, erythema, dry skin, and inflammation.[1-3] The condition is chronic and relapsing and often occurs in patients with a family history of the atopic triad (asthma, allergic rhinitis, and AD). Two main concepts have evolved to explain the pathogenesis of AD: excessive T-cell activation in response to an antigen and hyperstimulation of T cells by atopic Langerhans cells.[1,2,4] Prevalence of AD varies by geographic region. An analysis of AD among 155 collaborating centers in 56 countries reported prevalence rates ranging from <1% to 20%.[5] One report concerning schoolchildren in Oregon found 17% had AD, suggesting that a wide variation by locale is also probable within the United States.[6]

Societal and Patient Costs

Approximately 49% to 70% of childhood AD cases occur by 6 months of age, while 80% to 90% present by age 5.[3] Males and females are affected in equal proportion, and no differences have been found between children of different racial and ethnic backgrounds.[1] Psychological problems are a concern in treating children with AD,[7-9] and an Australian cross-sectional survey found that childhood AD has a profound impact on families.[10]

AD presents an economic burden to families, society, and the health care system. U.S. data indicate that direct medical costs, consisting of emergency room visits, outpatient treatment, physician office visits, and prescriptions for AD patients younger than 25 years totaled $364 million in 1990.[11] Another study, using 1997 and 1998 claims data from a private insurer and state Medicaid program, examined the third-party payer costs for AD and eczema, finding that costs ranged from $0.9 billion to $3.8 billion when projected across the total number of persons younger than 65 years. The authors concluded that the cost of AD is similar to diseases such as emphysema, psoriasis, and epilepsy.[12]

Families bear a substantial portion of the health care costs for AD. Two studies done in large managed health care organizations using claims data and patient/parent surveys came to similar conclusions: In the first, 962 AD patients were identified, of which almost half were children younger than 17 years.[13] Mean per-patient annual costs totaled $609, with the third-party payer covering only 24%, or $167 per patient. Third-party payer costs were almost entirely due to costs of office visits and prescription medications. About 50% of the total burden of illness was related to lost productivity; the remainder was paid directly by the patient or parent for treatments not covered by insurance.[13] The second study, which

focused exclusively on pediatric and adolescent patients, estimated that direct medical costs paid by the insurer accounted for 30% of the total financial burden for that organization's AD patients younger than 18 years.[14] The parental financial burden (which also included estimated costs of lost productivity) averaged $439 per year. These authors projected their data to estimate national costs. Assuming an AD prevalence of 12% to 16% of U.S, school-aged children, total costs for treatment of pediatric AD in the United States could range from $4.9 billion to $6.5 billion per year.[14]

Novel, Steroid-free Agents

Although topical steroids can be effective in AD treatment, their use is limited due to the potential for side effects, both local and systemic (Table 1). Several factors have driven the development of more effective, steroid-free therapies to treat AD. First, the evolving understanding of the pathogenesis of AD has allowed researchers to target specific steps in the inflammatory cascade.[4] Second, the limitations of topical corticosteroids are well known. The third driver is related to the second: patients and parents may be phobic about using steroids and, therefore, be noncompliant.[7,15,16]

Two effective, steroid-free treatments for AD have become available within the past 2 years. Tacrolimus ointment (Protopic 0.03% and 0.1%), a topical immunomodulator, became available in early 2001.[17] A similar but highly skin-selective cytokine inhibitor, pimecrolimus cream (Elidel 1%), became available in March 2002.[18]

Indications

Pimecrolimus is approved for mild-to-moderate AD, while tacrolimus is indicated for moderate-to-severe AD. Pimecrolimus cream 1% is indicated for all patients aged 2 years and older. The 0.03% strength tacrolimus ointment is recommended for children aged 2 to 15 years, and the 0.1% strength is recommended for adults. Both agents are indicated for the short-term and intermittent, long-term management of AD (eczema) in nonimmunocompromised patients, in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to, or are intolerant of, alternative, conventional therapies.[18,19]

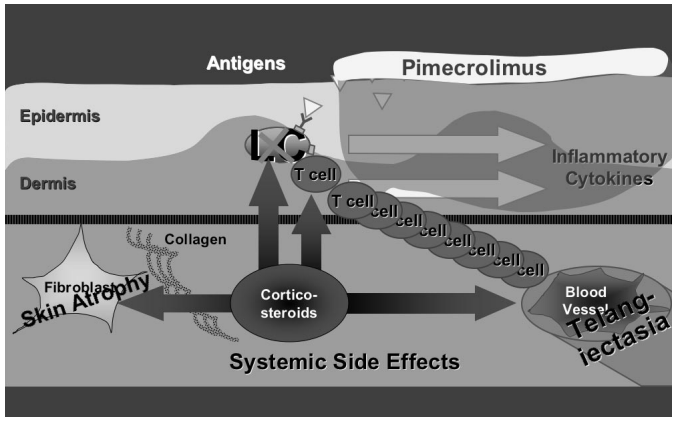
Pharmacology

The full mechanism of action of pimecrolimus has not been completely elucidated. However, inhibition of the calcium-dependent phosphatase, calcineurin, has been observed. Consequently, the drug inhibits T-cell activation by blocking the transcription of early cytokines. In addition, pimecrolimus inhibits the release of inflammatory cytokines and mediators from mast cells and basophils in vitro after stimulation by antigen/Ig (immunoglobulin) E.[20,21] Pimecrolimus has no effect on keratinocytes, fibroblasts, endothelial cells, Langerhans cells, the hypothalamus, or adrenal gland.[21]

TABLE 1 Side Effects Associated With Prolonged Topical Corticosteroid Therapy

Local Side Effects	Systemic Side Effects
Skin	• Hypothalamic-pituitary-adrenal axis suppression
• Atrophy	• Growth retardation/Failure to thrive
• Telangiectasia (thinning of epidermis)	• Cushing's syndrome
• Striae (stretch marks)	
• Dyspigmentation	
• Perioral dermatitis/acne	
• Hirsutism	
Eye (with treatment at eye area)	
• Glaucoma	
• Cataract	

FIGURE 1 Selective Effect of Pimecrolimus Versus Corticosteroids in Skin With Atopic Dermatitis



LC = Langerhans cells.

The mechanism of action and pharmacological profile of pimecrolimus differ markedly from corticosteroids. Figure 1 shows the mechanism of action of pimecrolimus versus corticosteroids. Pimecrolimus interferes with the inflammatory process by preventing release of cytokines without affecting other skin systems.

Pharmacokinetics

Preclinical pharmacokinetic studies indicated that pimecrolimus is highly absorbed into the skin but has little or no absorption into systemic circulation.[21,22] In 12 adults with extensive AD, 78% of 444 blood samples had pimecrolimus concentrations below the limit of quantification (0.5 ng/ml).[22] This skin-selective property makes pimecrolimus different from tacrolimus. Billich et al.[23] com-

pared the in vitro skin penetration and permeation of pimecrolimus and tacrolimus and 3 representative corticosteroids (betamethasone-17-valerate, clobetasol-17-propionate, and diflucortolon-21-valerate).[23] Drug concentrations of pimecrolimus and corticosteroids in human skin were found to be in the same order of magnitude. Permeation of pimecrolimus through human skin was, however, lower by factors of 70 to 10 as compared with the steroids. When pimecrolimus was compared with tacrolimus in human, pig, or rat skin, similar concentrations of the 2 compounds were measured in the skin, whereas permeation of pimecrolimus through skin was consistently lower by factors of 9 to 10. Lipophilicity was found to be highest for pimecrolimus, its octanol-water distribution coefficient being higher by factors of 8 and 25 to 450 than that of tacrolimus and the corticosteroids, respectively. The authors postulated that the low permeation of pimecrolimus may be explained by its higher lipophilicity (compared with tacrolimus and the corticosteroids) and higher molecular weight (compared with steroids). They concluded that pimecrolimus appears to have a favorable skin penetration/permeation profile, featuring a low degree of percutaneous absorption.[23] Work with animal models also indicated that pimecrolimus is less likely than tacrolimus to induce immunosuppression (as measured by graft/host rejection).[17,21]

Pimecrolimus may have a high affinity for the skin because of its highly lipophilic nature. That hypothesis is anecdotally supported by a small, 4-week study performed with 16 healthy volunteer subjects. In the randomized, double-blind, controlled trial, pimecrolimus 1% was compared with corticosteroid cream to determine skin atrophy effects.[24] Subjects applied the cream twice daily, 6 days a week, for 4 weeks. Skin thickness was evaluated by ultrasound, clinical signs of atrophy, and epidermis thickness. Topical steroid preparations caused a significant reduction in skin thickness, whereas the pimecrolimus and vehicle induced no skin thinning.[24]

While corticosteroids are readily absorbed through the dermis and into the systemic circulation, pimecrolimus penetrates the dermis only minimally; therefore, systemic absorption of pimecrolimus cream is consistently low. Preclinical investigations found that blood concentrations were minimal in children and infants. In 26 pediatric AD patients, aged 2 to 14 years with 20% to 69% body surface area involvement, blood concentration with twice-daily application averaged <3 ng/mL. The majority of blood samples were below the limit of quantification (0.5 ng/mL). This result was consistent (ranging from 0.1 ng/mL to 2.6 ng/mL) even with application on up to 92% of body surface area in 22 infants aged 3 to 23 months.[22,25]

Comparative Efficacy

The pimecrolimus clinical research program has now gathered extensive data in short- and long-term studies of patients with AD.[26-30] The program has focused primarily on children but has included infants and adults. Extensive pharmacokinetic profiling has been performed in patients down to 3 months of age.

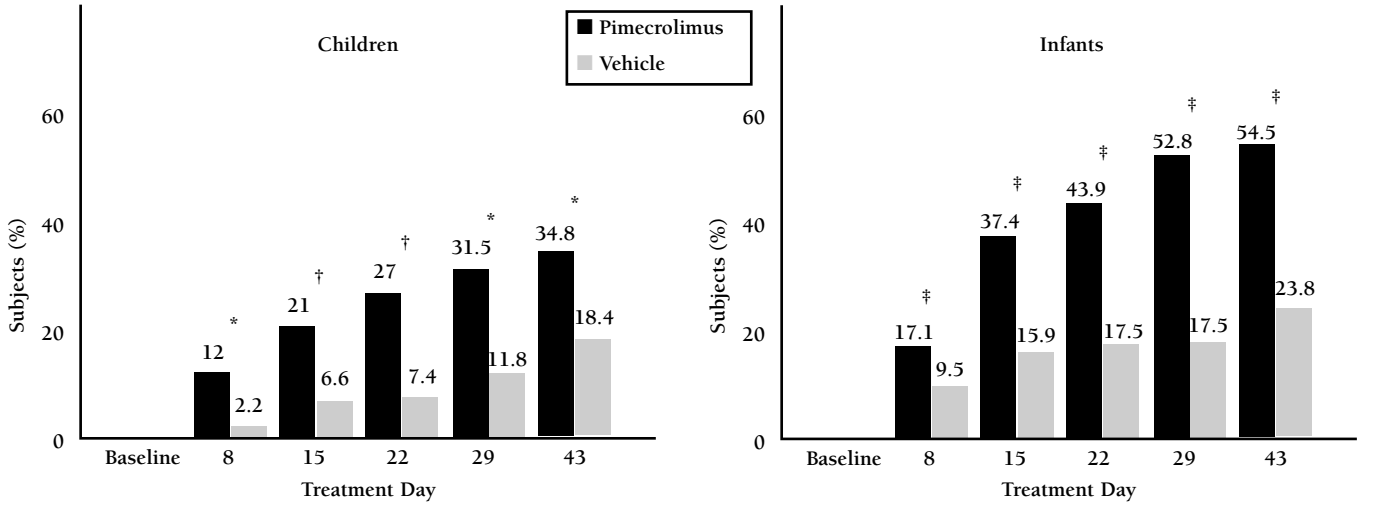
Short-term Studies

Pivotal data came from 3 short-term trials, the results from 2 trial groups (children and adolescents aged 2 to17 years [n=403], reported as pooled data by Eichenfield et al. in 2002),[27] and a trial with infants aged 3 to 23 months (n = 186), reported by Ho et al. in 2003.[26] These 3 study designs were identical, providing some justification for the use of pooled data to determine effects in children aged 2 to 17 years. The common study design consisted of 6 weeks of treatment in a randomized, placebo-controlled, double-blind phase, followed by an open-label extension of 20 weeks during which all patients received pimecrolimus treatment. In the double-blind phase, pimecrolimus was compared with a placebo vehicle; no corticosteroids were given. Six weeks of therapy in clinical practice is considered sufficient to obtain significant improvement in symptoms of AD. Without satisfactory response by 6 weeks, good practice indicates a need to reevaluate the patients. However, during trials with pimecrolimus, response was observed in a much shorter time frame.

At each visit, investigators assessed efficacy and safety using several measurements. Efficacy end points included the Investigator Global Assessment (IGA) score, the Eczema Area and Severity Index (EASI), severity of pruritus, and the subject's own assessment of disease control. (Dermatologists in clinical practice do not generally measure effectiveness through the use of instruments such as the IGA and EASI, but these are common clinical research tools.) The IGA score is based on a 5-point rating scale that rates severity of signs and symptoms of AD. A score of 2 or 3 indicates mild-to-moderate symptoms, e.g., mild erythema and papulation/infiltration, or 3, moderate erythema, papulation/infiltration. A rating of 5 is defined as very severe erythema, papulation/infiltration with oozing/crusting. The EASI measures body area affected by and the severity of 6 clinical signs of AD; the EASI is also expressed as a composite score of the 6 measures: edema, erythema, excoriation, lichenification, oozing, and scaling.[30,31] Hanifin et al. performed an evaluation to validate the reliability of the EASI scoring system by assessing inter- and intraobserver consistency.[31] Twenty adults and children with AD were evaluated: cohort 1 (10 patients aged ± 8 years) and cohort 2 (10 patients aged < 8 years). The EASI was utilized by 15 dermatologist evaluators to assess AD in cohort 1 and cohort 2 on 2 consecutive days.

The authors found that overall intraevaluator reliability of the EASI was in the fair-to-good range. Interevaluator reliability analyses indicated that the evaluators assessed the patients consistently across both study days. The authors concluded that the EASI can be learned quickly and utilized reliably in the assessment of severity and extent of AD and that these results support the use of the EASI in clinical trials of therapeutic

FIGURE 2 Short-term Studies in Infants[26] and Children:[27] Percentage Rated Clear or Almost Clear by IGA Score (0 or 1)



*$P \leq .05$. †$P \leq .001$. ‡$P < .001$. *Success: IGA (Investigator Global Assessment) score = 0 (clear) or 1 (almost clear).*

agents for AD.[31] End points were expressed as percentage of change from baseline in IGA and EASI scores.

The pooled data study included 403 pediatric patients aged 2 to 17 years who had AD affecting at least 5% of total body surface area.[27] Children had to have a baseline IGA score of 2 or 3, corresponding to mild-to-moderate disease. Significant improvement in primary and secondary efficacy measures occurred. For example, as measured by IGA scores at 6 weeks, 34.8% of those using pimecrolimus had ratings of 0 or 1, indicating that AD was clear or almost clear.[27] The placebo group, on the other hand, reported 18.4% of 0 or 1 scores. As shown in Figure 2, the study medication had a rapid onset of action. By day 8 of treatment, a statistically significant difference was noted between the pimecrolimus and vehicle (placebo) groups ($P = <0.05$). Figure 2 also shows that similar results were derived from Ho's study of infants aged 3 to 23 months, which was also randomized, double-blind, and placebo-controlled.[26] At 6 weeks, 55% of the pimecrolimus group versus 24% of the vehicle group were clear or almost clear of AD. Results were statistically significant during each week of the study.

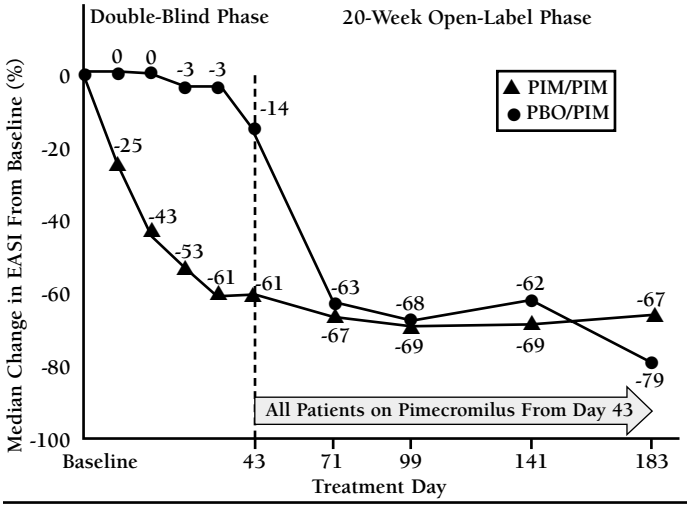
In both the pediatric and infant clinical trials, patients reported significant pruritus relief in the first week of treatment. At the end of 6 weeks, 54% of children using pimecrolimus and 32.5% of those using the vehicle reported pruritus relief.[27] Similar results were found in infants: at 6 weeks, 72% versus 33% of pimecrolimus- and vehicle-treated patients, respectively, reported pruritus relief ($P<0.005$).[26] EASI scores also improved significantly. Pediatric patients on pimecrolimus had a median improvement in EASI scores from baseline of 61% at 6 weeks. After the placebo-controlled period, children receiving the vehicle were switched to pimecrolimus during a 20-week open-label continuation phase. Figure 3 shows that, beginning at 6 weeks, those in the vehicle arm who began treatment with pimecrolimus experienced a median improvement in EASI scores from 14% to 63% at day 71 and had a 79% improvement at 6 months.[27]

Infants experienced even greater improvement in EASI scores. At the end of 6 weeks, infants' EASI scores improved by 81.6% compared with 4% in the control group ($P \leq .001$). Beginning at 6 weeks, infants previously receiving the vehicle began pimecrolimus treatment. Between day 43 and day 71 (4 weeks of treatment), infants using pimecrolimus experienced an 81% improvement in EASI scores.[26]

In young children, and especially in infants, facial involvement of AD is common.[1] Steroids, however, can be used only sparingly on the face and neck because of side effects that include skin thinning. In the infant studies, investigators specifically looked at improvement of the EASI scores in the head and neck area.[26] As shown in Figure 4, the median percentage improvement in overall EASI scores was significant at all post-baseline visits to vehicle ($P<0.001$). The median percentage improvement in the head and neck area was substantial.

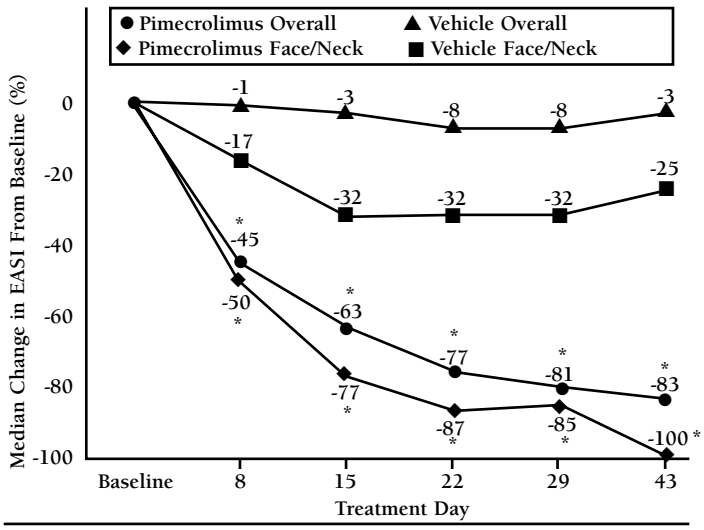
Kempers et al. evaluated pimecrolimus cream 1% and tacrolimus ointment 0.03% in pediatric patients with moderate AD.[32] In this study, 141 patients (aged 2 to 17 years) were randomized to treatment with pimecrolimus cream 1% (n = 71) or tacrolimus ointment 0.03% (n = 70) twice daily for 6 weeks. At day 4, local, application-site reactions were less common and

FIGURE 3 Pediatric Studies: Median Change (%) in Eczema Area and Severity Index (EASI) With Pimecrolimus During 6-Week Open-Label Phase[27]



PIM = pimecrolimus 1% cream; PBO = placebo cream.

FIGURE 4 Infant Study: Median Percentage Improvement in Overall and Head/Neck Eczema Area and Severity Index (EASI)[26]



** Change in EASI significant at all postbaseline visits, P <.001.*

of shorter duration with pimecrolimus than with tacrolimus. The incidence of erythema/irritation was 8% (6 of 71) with pimecrolimus, compared with 19% (13 of 70) with tacrolimus (P = 0.039) While the incidence of warmth, stinging, and burning was similar in both groups, reactions lasting >30 minutes were fewer with pimecrolimus (0%, 0 of 14) than with tacrolimus (67%, 8 of 12; $P < 0.001$). Efficacy was similar in both treatment groups at day 43. The authors concluded that pimecrolimus cream 1% had better formulation attributes and local tolerability than tacrolimus ointment 0.03% while providing similar efficacy and overall safety in pediatric patients with moderate AD.[32] This head-to-head study was sponsored by the manufacturer of pimecrolimus.

Long-term Studies

Infants and Children/Adolescents: Results of long-term studies of pimecrolimus are equally encouraging. The objective of the long-term management studies was to evaluate the 6- and 12-month efficacy and safety of a pimecrolimus-based, long-term management strategy versus conventional treatment.[28,29] All disease severities were allowed, and medium potency corticosteroids were used to control severe flares in both groups. Figure 5 illustrates the study design. All patients used emollients. At the first signs and symptoms of AD, pimecrolimus or the vehicle was applied to the affected areas.

The primary efficacy end point was the number of flares at 6 months. Secondary measures included the number of flares at 12 months and the number of flares by disease severity at baseline. Efficacy was also measured by the reduction in corticosteroid use and the EASI score. Safety end points included number and type of adverse events, physical examination, and laboratory evaluations performed at screening, 6 months, and study end.

Significant improvement occurred with pimecrolimus versus conventional therapy. As shown in Figure 6, 68% of infants and 61% of children/adolescents treated with pimecrolimus reported no flares at 6 months. At 12 months, 57% of infants and 51% of children/adolescents had no flares.[28,29]

Long-term use of steroids among children/adolescents was significantly reduced by pimecrolimus treatment.[28] At 6 months, 66% of pimecrolimus-treated patients reported 0 days of steroid therapy compared with 38% treated with conventional therapy. Figure 7 shows steroid use in children/adolescents at the end of 12 months. Fifty-seven percent of the pimecrolimus group had 0 days of corticosteroid therapy, whereas only 32% of the conventional treatment group had 0 days of steroids. In the pimecrolimus group, four fifths (83%) of patients required 14 days or fewer of corticosteroid therapy compared with 60% of those on conventional therapy.[28]

Adults: A 6-month, randomized, controlled trial assessed the efficacy and safety of pimecrolimus in adults with moderate-to-severe AD.[30] A sample of 192 patients was randomized to either pimecrolimus or placebo cream. Pimecrolimus proved significantly more effective than placebo ($P \leq .001$), as measured by percentage of days requiring second-line rescue therapy. Fifty-eight percent of pimecrolimus-treated versus 30% of placebo-treated patients reported 0 flares by study end.[30]

Adverse Events

The potential toxicity of pimecrolimus has been studied extensively. No evidence has been noted for reproductive toxicity or carcinogenicity in mice at relevant doses or for photocarcinogenicity and mutagenicity in mouse models.[21,25] Label "warnings" include the results of rat dermal carcinogenicity studies using pimecrolimus in which there were statistically significant increases in the incidence of follicular cell adenoma of the thyroid, but the doses of pimercolimus cream were 1.5 to hundreds of times the maximum recommended human dose based on area under the curve comparisons).[33] Dermatotoxicity studies show no cumulative irritancy, sensitization potential, phototoxicity, photoallergy, or skin atrophy in mouse models.[21,25]

Adverse-event profiles from short-term clinical trials were comparable in children and infants.[26,27] Most adverse events were mild or moderate and representative of typical childhood illnesses. No clinically relevant, drug-related systemic effects occurred. Upper respiratory tract infection was the most commonly reported adverse event (14.2% pimecrolimus versus 13.2% vehicle). The percentage of children and adolescents experiencing an adverse event of any kind was similar between those two groups. Application site reactions were less common in pediatric patients receiving pimecrolimus (10.4%) than those receiving the vehicle (12.5%).[27] A warmth or burning sensation was mostly mild to moderate and transient. Pruritus occurred in 1.1% versus 1.5% of control-treated patients. In short-term pediatric trials of tacrolimus 0.03%, pruritus occurred in 41% versus 27% of control-treated patients.[34] Patients in pimecolimus infant studies showed a similar lack of significant difference in the incidence of adverse events between pimecrolimus and placebo as those in pediatric studies.[26]

In long-term pediatric trials, no significant differences in adverse events were found between pimecrolimus and conventional therapy groups. Both groups had similar rates of application site reactions (10.5% versus 9.3%, pimecrolimus versus control), viral skin infections (12.4% versus 6.3%, pimecrolimus versus control), and bacterial skin infections (14.2% versus 30.9%, pimecrolimus versus control).[28] Pruritus occurred in 1.8% versus 0% in the control group. In the infant studies, there was a similar lack of significant difference in incidence of adverse events between pimecrolimus and control groups.[29]

In long-term studies of tacrolimus, 0.1%, bacterial skin infections occurred in 11% of both pediatric and adult patients; viral infections occurred in 14% of pediatric and 8% of adult patients. Pruritus occurred in 25% of both pediatric and adult patients.[34]

The most common adverse effects in all trials were application site reactions, such as itching or a burning sensation. As shown above, with use of pimecrolimus, incidence of burning sensation was low and occurred almost equally in the pimecrolimus and control groups (10.5% versus 9.3%, respectively).[28] During tacrolimus clinical trials, with use of a significantly lower-strength ointment (tacrolimus 0.03%), burning occurred in 43% and 46% of pediatric and adult patients, respectively.[34,35] With use of the 0.1% strength tacrolimus ointment, burning occurred in 58% of adults.[35] It is not considered good science to make cross-trial comparisons, but there are no head-to-head comparative trials to rigorously test the differences in the side-effect profiles of these two products.

FIGURE 5 Study Design of Long-term Evaluations of Pimecrolimus Use in Atopic Dermatitis[28,29]

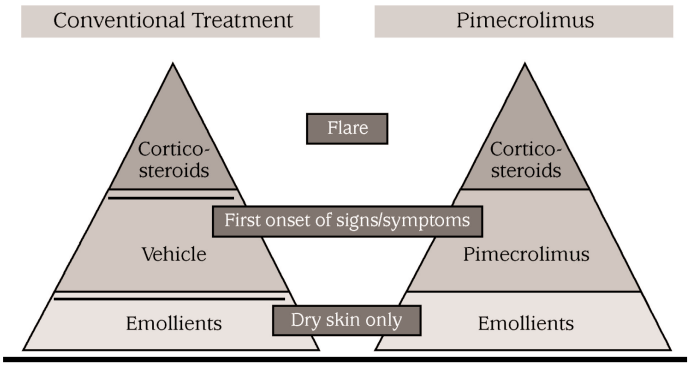
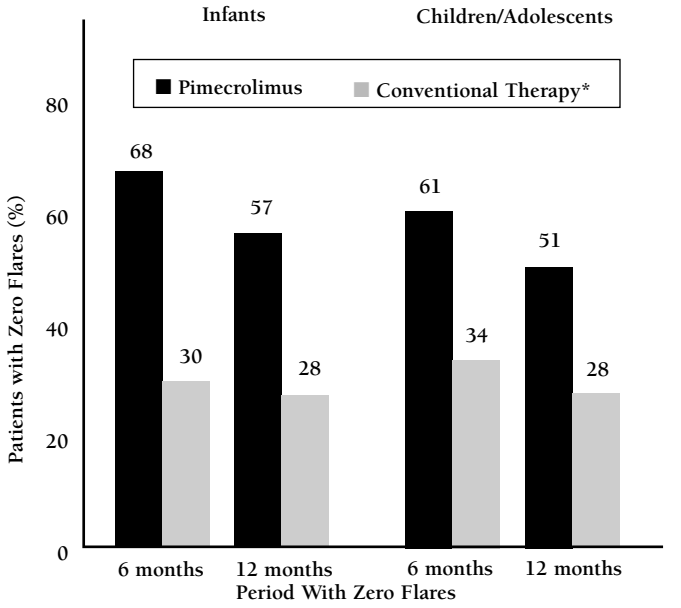


FIGURE 6 Percentage of Infants[29] and Children/Adolescents[28] Having Zero Flares With Pimecrolimus Over 12 Months

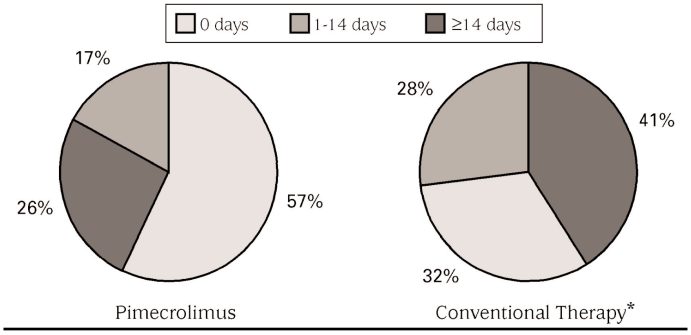


† Conventional therapy: emollients for dry skin and moderately potent topical corticosteroids for flares of atopic dermatitis.

Drug Interactions

Interactions between pimecrolimus and systemically administered medication are considered unlikely due to minimal absorption.

FIGURE 7 Use of Corticosteroids in Children/Adolescents During 12 Months of Treatment: Pimecrolimus Versus Conventional Therapy [28]



** Conventional therapy: emollients for dry skin and moderately potent topical corticosteriods for flares of atopic dermatitis.*

TABLE 2 Direct Drug Costs for Topical Therapeutic Alternatives for Atopic Dermatis

Agent	Cost*
Pimecrolimus 1% 30 grams	$57.84
Pimecrolimus 1% 60 grams	$108.04
Tacrolimus 0.03% 30 grams	$59.53
Tacrolimus 0.1% 30 grams	$61.72
Tacrolimus 0.1% 60 grams	$124.57
Clobetasol propionate cream 0.05% 15 grams	$10.99
Clobetasol propionate cream 0.05% 30 grams	$15.53
Desonide cream 0.05% 15 grams	$10.99
Desonide cream 0.05% 60 grams	$17.99
Hydrocortisone butyrate 0.1% 15 grams (Locoid)	$35.10
Hydrocortisone butyrate 0.1% 45 grams (Locoid)	$72.89
Hydrocortisone butyrate 0.1% 30 grams (Florasone, OTC)	$5.73

** Purchase price from www.drugstore.com on December 18, 2004.*
OTC = over-the-counter.

Neither pimecrolimus nor tacrolimus should be used concomitantly with topical anti-inflammatories, including steroids, or with other immunosuppressives. Caution should be used in concomitant administration with the known CYP3A family of inhibitor drugs, such as erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers, and cimetidine.

Dosing and Administration

Pimecrolimus can be used on all skin surfaces, including the head, neck, and interiginous areas. It is safe under clothing and washes off with soap and water. Moisturizers can be used after applying the medicated cream. There are no restrictions on the amount applied, the body surface area treated, or the duration of treatment.

A thin layer of pimecrolimus cream should be applied to the affected skin and rubbed in gently and completely. Pimecrolimus cream may be used twice daily as long as symptoms persist but should be discontinued if signs and symptoms of eczema disappear. If symptoms persist beyond 6 weeks, the patient should be reevaluated. Application of tacrolimus ointment is similar; however, treatment should be continued for 1 week after signs and symptoms clear. Neither product is approved for use under occlusive dressings.

Neither pimecrolimus nor tacrolimus should be used on areas of the skin affected by a viral or clinical infection. The infection should be cleared before beginning therapy. No controlled studies have been conducted with pregnant women; therefore, neither agent is recommended for use by pregnant or lactating females.

Availability

Pimecrolimus cream 0.1% is available by prescription only and is available in tubes of 30 grams, 60 grams, and 100 grams for patients 2 years and older. Tacrolimus ointment 0.03% and 0.1% are both available in tubes of 30 grams, 60 grams, and 100 grams. Only the 0.03% ointment is indicated for pediatric use and is limited to children 2 years and older. Both products should be stored at room temperature (59 to 86 degrees Fahrenheit).

Costs of Therapy

The costs of therapy are impacted by many factors. Pimecrolimus and tacrolimus are priced similarly when compared in terms of direct drug cost, but both have a much higher direct drug cost compared with the topical corticosteroids, most of which are available in generic form (Table 2). Hydrocortisone butyrate 0.1% is available over the counter (OTC; e.g., Florasone) and by prescription (e.g., Locoid), and both prices are included for comparative purposes. Desonide is similar in potency to hydrocortisone, is not available OTC, but is available in generic form. Clobetasol is higher in potency compared with desonide and hydrocortisone butyrate, is not available OTC, but is available in generic form. Clobetasol suppresses the hypothalamic-pituitary-adrenal axis at doses as low as 2 grams per day, and therefore may not be the best choice for children.[36]

Quality-of-Life Assessments

AD impairs quality of life for those affected and for their caregivers. For example, one study assessed 239 AD patients aged 4 to 70 years.[37] Using various quality-of-life measures, researchers found that AD was associated with deficits in social functioning and psychological well-being. Greater health-related quality-of-life decrements were associated with more

severe disease. These researchers also found that patients with AD had poorer mental health scores than those with diabetes or hypertension. Another study found that AD patients rated their health at only 73% of perfect health.[38] Quality of life improves with successful treatment of AD for pediatric patients and their parents.[39] Parents reported that they were able to get more sleep, devote less time to treatments, and spend less time worrying. Because pimecrolimus effectively reduces flares and reduces the need for steroid use, it can be assumed that its use will also positively affect quality of life for patients and families.

Summary

Pimecrolimus is a cell-selective inhibitor of inflammatory cytokines. Because it has low absorption through the skin, it is not associated with the atrophogenic effects to the skin found with the corticosteroids and has low potential to impair the HPA. Pimecrolimus blood levels remain consistently low after repeated topical application, and no clinically relevant drug-related systemic effects have been reported among the 8,000 patients treated in clinical trials to date.[40]

Pimecrolimus is a safe and effective steroid-free treatment for AD. Consistently positive results have been found with pimecrolimus treatment in infants, children, adolescents, and adults. Unlike tacrolimus, a single strength is recommended for use in all ages. Tacrolimus 0.03% is indicated for children 2 to 17 years and the 0.1% strength is indicated for adults. When used at the first signs and symptoms of AD, pimecrolimus reduces flares by preventing disease progression to flare. In clinical trials comparing pimecrolimus with placebo or topical corticosteroids, no significant differences between treatment groups were found in percentage or type of adverse events, infections, and application site reactions.

Tacrolimus has demonstrated efficacy in more severe patients while pimecrolius data support use for mild-to-moderate AD patients. Both offer alternative treatment to steroids. Pimecrolimus's safety, efficacy, and positive impact on quality of life make it an important addition to the physician's treatment options, and available clinical data show excellent results in infants and in use on the face and neck. Pimecrolimus should be regarded as an effective, steroid-sparing therapy for mild-to-moderate AD in patients of all ages. Although pimecrolimus and tacrolimus have U.S. Food and Drug Administration indications to treat children as young as 2 years old, pimecrolimus has published evidence that it is effective in infants as young as 3 months old.[26] It is appropriate as a first-line agent as well as for long-term, intermittent therapy.

Recent case studies indicate that pimecrolimus may have many potential applications, by both topical and oral administration. In 2002, Crutchfield reported a case of effective topical treatment for facial seborrheic dermatitis with pimecrolimus.[41] Topical treatment may also have a role in such diverse conditions as contact dermatitis, hand dermatitis, acne and steroid rosacea, inverse psoriasis, vitiligo, intertrigo, facial dermatitis, and blepharitis of various etiologies.

Also in 2002, Rappersberger et al. reported a phase I/II randomized, double-blind, placebo-controlled, multiple rising-dose, proof-of-concept study in which psoriasis patients were treated with oral pimecrolimus or placebo.[42] Clear clinical efficacy occurred in patients receiving 20 mg or 30 mg of pimecrolimus twice daily. Psoriasis Area (PI) and Severity Index (SI) were reduced by 60% and 75%, respectively. No notable clinical, laboratory, kidney function, or immunologic side effects were reported.

Considering the economic burden of the disease, the relative and total costs associated with available treatment options are important to patients and their families as well as to insurers. The preliminary data, which were derived through studies of cost impact within managed care organizations, indicate that pimecrolimus use may have the potential to reduce overall costs of the disease. Although preliminary, these economic data are encouraging since they support the opinion that using new, more effective treatments for AD can lessen reliance on corticosteroids.

DISCLOSURES

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