Pharmacology and Treatment

Dermatology

Dermatology 2006;213:313–318
DOI: 10.1159/000096195

Received: December 27, 2005
Accepted: May 10, 2006

Benefits from the Use of a Pimecrolimus-Based Treatment in the Management of Atopic Dermatitis in Clinical Practice

Analysis of a Swiss Cohort

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Key Words
Atopic dermatitis · Eczema · Elidel · Pimecrolimus cream 1%

Abstract

Background: Controlled studies established the efficacy and good tolerability of pimecrolimus cream 1% for the treatment of atopic dermatitis but they may not reflect real-life use. ***Objective:*** To evaluate the efficacy, tolerability and cosmetic acceptance of a pimecrolimus-based regimen in daily practice in Switzerland. ***Methods:*** This was a 6-month, open-label, multicentre study in 109 patients (55% ≥18 years) with atopic dermatitis. Pimecrolimus cream 1% was incorporated into patients' standard treatment protocols. ***Results:*** The pimecrolimus-based treatment was well tolerated and produced disease improvement in 65.7% of patients. It was particularly effective on the face (improvement rate: 75.0%). Mean pimecrolimus consumption decreased from 6.4 g/day (months 1–3) to 4.0 g/day (months 3–6) as disease improved. Most patients (74.1%) rated their disease control as 'complete' or 'good' and 90% were highly satisfied with the cream formulation. ***Conclusion:*** The use of a pimecrolimus-based regimen in everyday practice was effective, well tolerated and well accepted by patients.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder [1, 2], which commonly affects both children and adults [1, 3–7] and imposes substantial burdens on patients, their families and the health care system [8, 9]. In Switzerland, the lifetime prevalence of AD is about 13% [4, 5]. Persistence of the diseases in adulthood has been reported to occur in more than 60% of Swiss patients suffering from AD in infancy [6].

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Topical corticosteroids (TCS) have been considered for many years the first-line anti-inflammatory treatment for AD [10], but their application for prolonged periods is associated with the occurrence of local adverse effects, particularly skin atrophy [10, 11]. In addition, extensive use of TCS in young paediatric patients may cause significant systemic adverse effects due to the percutaneous absorption of these drugs and consequent suppression of the hypothalamic-pituitary-adrenal axis [11, 12]. As AD usually assumes a chronically relapsing course [1–3], the necessary restrictions in TCS use for the safety reasons mentioned above do not allow a satisfactory control of the disease in the long term. Furthermore, patients' corticophobia and low compliance with treatment [13, 14] have in fact reduced the effectiveness of TCS in the management of AD in many cases.

Pimecrolimus cream 1% (Elidel®, SDZ ASM 981) is a non-steroid, anti-inflammatory, topical calcineurin inhibitor developed for the treatment of chronic skin disorders such as AD [15, 16]. Topically applied pimecrolimus specifically inhibits the release of inflammatory cytokines and mediators from T cell and mast cells in the skin [15–18]. In contrast to TCS, it does not induce skin atrophy, is minimally absorbed, and does not affect the hypothalamic-pituitary-adrenal axis [15, 16]. Large, multicentre, controlled studies in paediatric and adult patients with AD have demonstrated that treatment with pimecrolimus cream 1% induces a rapid and sustained improvement of symptoms [15, 16, 19, 20], prevents flares [15, 16, 19, 20], reduces the need for TCS [15, 16, 19], and is tolerated well [15, 16, 19, 20]. Conclusive data about the long-term safety of topical calcineurin inhibitors will only be obtained after completion of ongoing epidemiological programmes. Nonetheless, the intermittent use of pimecrolimus cream 1% for up to 2 years, in about 20,000 patients treated in clinical trials, has not been associated with systemic immunosuppression or with immunosuppression-related diseases that are known to occur following sustained, systemic immunosuppression with oral immunosuppressants, such as cyclosporine A and corticosteroids [18]. Unwanted effects of TCS such as tachyphylaxis and disease rebound upon discontinuation have not been observed with pimecrolimus cream 1% [21]. However, controlled clinical trials, with their stringent criteria, may not reflect real-life use. This report provides information on the effectiveness, safety, tolerability and acceptability of a pimecrolimus-based treatment for AD in daily practice in Switzerland.

Patients and Methods

This was a 6-month, open-label, single-arm, multicentre study involving patients aged ≥3 months with the diagnosis of AD of any severity. Patients were included from August 2001 to March 2002. Physicians incorporated pimecrolimus cream 1% into their AD treatment protocols. The patients were instructed to apply the cream twice daily to all affected areas until complete clearance of inflammation was achieved and pruritus had ceased. They were allowed to stop treatment on cleared lesions while continuing to apply study medication on skin areas of persisting inflammation, and to restart treatment on cleared lesions as soon as they observed recurrence of the inflammatory process. The use of emollients was encouraged, antimicrobial agents were allowed to treat skin infections, and TCS could be used to treat severe flares. Efficacy was evaluated at each visit following the baseline assessment (weeks 1, 4, 8, 16, 24 of the treatment period). The investigators ranked the disease severity for the whole body and, separately, for the face by using the Investigators' Global Assessment (IGA) scoring system [15], a 6-point scale ranging from 0 (clear) to 5 (very severe disease). Disease improvement was defined as a reduction in IGA score of at least 1 compared with the baseline score. For pruritus assessment, patients or their caregivers ranked the intensity of itching/scratching in the 24 h preceding each visit by means of a 4-point scale ranging from 0 (absent) to 3 (severe) [15]. Patients or their caregivers also recorded their assessment of disease control during the 7 days prior to each visit using a 4-point scale from 0 (complete disease control) to 3 (uncontrolled disease). The cosmetic acceptability of treatment was evaluated by questionnaire [22] at week 8. Safety and tolerability were examined by monitoring adverse events and by assessing physical condition at each visit. The study was approved by the institutional ethics committees and all patients or legal guardians provided signed informed consent.

Data analysis was based on all patients who applied study medication at least once and was performed using descriptive statistical methods. Missing post-baseline efficacy measurements were imputed using the last-observation-carried-forward approach. All patients who had IGA or pruritus scores of 0 at baseline were excluded from the whole body IGA, facial IGA and pruritus analyses, respectively.

Results

Patients and Treatment

A total of 110 patients were recruited in 8 centres in Switzerland: 109 patients (92.7% Caucasians) received at least one application of study medication. The mean age was 20.9 years (range: 6 months to 70 years) and 55% of patients were adults (table 1). The majority of patients had mild or moderate AD at baseline, as assessed by the whole body IGA scores (table 1). A total of 96 patients (88.1%) completed the study and 13 (11.9%) discontinued prematurely. Reasons for discontinuation were lost to follow-up in 6 patients, unsatisfactory therapeutic effect in

Table 1. Baseline demographic and patient characteristics

Total patients	109
Age, years	
Mean (range)	20.9 (0.5–70.0)
Age distribution, n (%)	
<2 years	16 (14.7)
2–12 years	22 (20.2)
13–17 years	11 (10.1)
≥ 18 years	60 (55.0)
Gender, n (%)	
Male	58 (53.2)
Female	51 (46.8)
Whole body IGA, n (%)	
0 = clear	1 (0.9)
1 = almost clear	7 (6.4)
2 or 3 = mild or moderate disease	77 (70.6)
4 or 5 = severe or very severe disease	24 (22.0)
Facial IGA, n (%)	
0 = clear	13 (12.0)
1 = almost clear	17 (15.6)
2 or 3 = mild or moderate disease	54 (49.5)
4 or 5 = severe or very severe disease	25 (22.9)
Pruritus score, n (%)	
0 = absent	3 (2.8)
1 = mild	35 (32.1)
2 = moderate	39 (35.8)
3 = severe	32 (29.4)

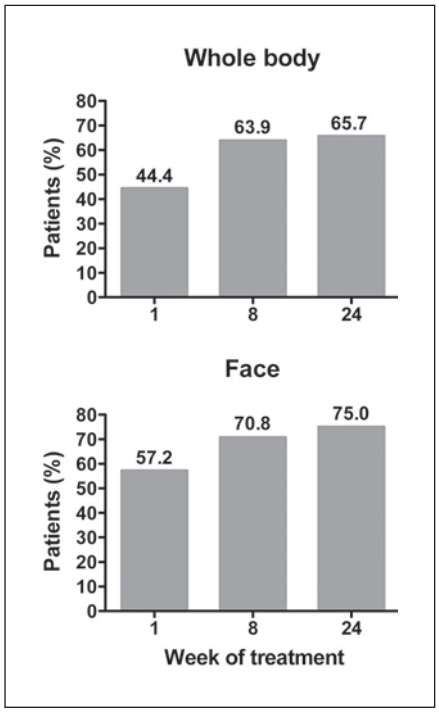

Fig. 1. Improvement rates for the whole body and the face by week of treatment. Any reduction in the whole body and facial IGA score from baseline defined whole body and facial improvement, respectively. All patients with a whole body and facial IGA score of 0 at baseline (table 1) were excluded from the whole body IGA and facial IGA analyses, respectively. Whole body improvement: n = 108; facial improvement: n = 96.

5 patients, withdrawal of consent in 1 patient, and adverse events in 1 patient.

The overall exposure to pimecrolimus cream 1%, as expressed by the mean number of treatment days, was 160.8 days (SD = 50.1 days). Drug consumption substantially decreased as disease improved: the mean amount of cream applied daily was 6.4 g (SD = 8.3 g) during the first 3 months and 4.0 g (SD = 6.2 g) during the last 3 months of the study. About 90% of patients used emollients on a regular basis. The predominant concomitant medications were TCS. At baseline, they were used by 45.0% of patients. The proportion of patients who used TCS at least once during the treatment period progressively decreased from 39.5% at week 1 to 28.6% at week 24. The most frequently used TCS were mometasone furoate at entry and mometasone furoate and fluticasone propionate during the treatment period. Other concomitant medications were topical antibiotics and systemic antihistamines.

Efficacy and Acceptability

The pimecrolimus-based treatment produced AD improvement in the majority of patients (fig. 1). The proportion of patients experiencing a decrease in whole body IGA score compared with the baseline score was high at week 1 and continued to increase throughout the course of the study (fig. 1). AD improvement rates were comparable in adult and paediatric patients: at week 24, the whole body IGA score decreased from baseline in 67.0% of adults and in 65.0% of paediatric patients. The improvement rate was particularly high for facial lesions (fig. 1), with similar results in adult (77.0%) and paediatric patients (71.0%) at the end of the study. On the basis of the whole body IGA score at baseline, 22.0% of patients had a severe eczema (IGA score of 4 or 5) before the incorporation of pimecrolimus cream 1% into their individual treatment regimen (table 1). During treatment, the proportion of patients with severe eczema decreased to 11.0% at week 1 and to 9.1% at week 4, and remained less than 7.5% at weeks 8 and 24. A representative example of the beneficial effects of the pimecrolimus-based regimen is shown in figure 2.

Fig. 2. This patient was a 57-year-old businessman with AD since adolescence. He had not used emollients and had phobia towards TCS. At inclusion in the study, active AD lesions covered about 80% of his body surface area. The pictures demonstrate the rapid and impressive improvement of eczema on the patient's hands and legs. After 8 weeks of treatment, residual AD lesions involved only 8% of the patient's body surface area. The use of pimecrolimus cream 1% decreased from 80 g/week during the first week of treatment to 50 g/week at week 16, when AD lesions were still present only on 2% of the patient's body surface area.

The rapid onset of efficacy of the pimecrolimus-based regimen was also reflected in early improvement of the pruritus score in the majority of patients: while 65.2% of patients reported moderate to severe pruritus at baseline (table 1), 57.7% of patients had no or only mild pruritus after the first week of treatment. The proportion of patients with absent or mild pruritus further increased to 70.8% at week 24.

After 6 months of treatment with the pimecrolimus-based regimen, 74.1% of the patients rated their disease control as 'complete' or 'good', compared with 26.9% at baseline. Moreover, 61.0% of paediatric patients and 67.0% of adult patients noted that the level of disease control had improved during the treatment period in comparison with the level of disease control at baseline.

After 8 weeks of treatment, 90% of patients rated pimecrolimus cream 1% as 'good' to 'excellent' in terms of spreadability, ease of rub-in, ease of application and non-sticky feel. In addition, 84% of patients rated pimecrolimus cream 1% as 'good' to 'excellent' in terms of suitability for use on sensitive facial skin. Overall, 95% of patients would continue to use pimecrolimus cream 1% for the treatment of AD and would tend to recommend pimecrolimus cream 1% to other patients with AD.

Safety and Tolerability

The only systemic adverse event reported by more than 1% of patients was cough (1.8%) and no case was considered to be related to treatment. The most frequent adverse event was application site burning, reported by 7 patients (6.4%). In most cases, this local reaction was mild or moderate, occurred early in the treatment period, and disappeared after a few days. Application site burning was also the adverse event most frequently considered to be treatment related. Other non-systemic adverse events reported by more than 1% of patients were erythema (4.6%), herpes simplex infection (2.8%), contact dermatitis (1.8%), folliculitis (1.8%) and eczema herpeticum (1.8%). The majority of these events were mild or moderate, with the exception of one case of contact dermatitis, which was severe

and led to premature discontinuation, and one case of eczema herpeticum in a 2-year-old child, which was reported as a treatment-related serious adverse event but resolved quickly with appropriate therapy (oral acyclovir). The two additional serious adverse events were anaphylactic shock due to food allergy in a 46-year-old patient and hospitalisation for treatment of a reproductive tract disorder in another 46-year-old woman.

Discussion

This report provides the first data on the effectiveness and tolerability of pimecrolimus cream 1% in the real-life treatment of AD in both adult and paediatric patients. The results are important as AD is a common chronically relapsing disease in children as well as in adults [1, 6].

The use of pimecrolimus cream 1% was evaluated by assessing parameters that are known to influence therapeutic decision in clinical practice, such as efficacy, safety, tolerability and treatment acceptability. Integration of pimecrolimus cream 1% into the individual treatment regimen, which also included the regular use of emollients, resulted in a substantial improvement of the signs and symptoms of AD in the majority of patients, irrespective of age. In over 57% of patients, pruritus relief and improvement of the skin lesions on the face were already observed within the first week of treatment. The response rate to the pimecrolimus-based regimen continued to increase thereafter and drug consumption substantially decreased as disease improved.

During the 6-month treatment period, the number of patients experiencing severe eczema was reduced to one third compared with baseline, and more than 60% of all patients never used TCS between week 1 and week 24. This underlines the fact that the majority of patients were free of severe exacerbations (major flares) of AD during that period. The beneficial effect of the pimecrolimus-based regimen was clearly perceived by the patients, as the majority of them reported an improved control of their AD. Overall, these data confirm the effectiveness of pimecrolimus cream 1% in the long-term control of AD as previously demonstrated in double-blind controlled clinical trials [15, 16, 19, 20].

In paediatric and adult patients, the disease improvement rates were comparable and in both groups the reduction in disease severity was more frequently observed on the face than on other body regions. In this respect, our results are consistent with the findings of a previous clinical trial conducted in children and adolescents with AD [23]. The fact that the pimecrolimus-based treatment was particularly effective on the face is important because TCS should not be used on body regions where the skin is particularly thin and more susceptible to the atrophogenic effects of TCS. It is also well known that patients are particularly reluctant to use TCS on the face because of the high risk of skin atrophy and other local adverse effects [13, 14]. Therefore, the pimecrolimus-based regimen can fulfill a key need among patients with AD.

The tolerability profile of the pimecrolimus-based regimen was good and consistent with the tolerability profile of pimecrolimus cream 1% established in the controlled clinical trials [15, 16, 19, 20]. There were no unexpected adverse events and no systemic adverse events suspected to be related to treatment. Skin burning was the most frequently reported treatment-related adverse event. This local reaction was transient and mild or moderate in the majority of the affected patients, and did not lead to discontinuation of treatment.

In AD, the beneficial effect of a given treatment on the course of the disease is not only related to the efficacy and tolerability of that treatment but also depends on patients' compliance [8]. While compliance can be controlled in clinical trials, in daily practice this is influenced by patients' satisfaction with the treatment modality, as demonstrated for TCS [13, 14]. Our data indicate that most patients were highly satisfied with the pimecrolimus cream 1% formulation and would continue to use this treatment or would recommend it to someone else. This represents another important advantage offered by pimecrolimus cream 1% in the long-term management of AD in comparison with TCS [13, 14].

In conclusion, the results of this analysis demonstrate that the use of pimecrolimus cream 1% for the treatment of AD in everyday clinical practice in Switzerland was effective, well tolerated and highly accepted. The introduction of pimecrolimus cream 1% into the topical treatment protocol was not only associated with rapid symptom relief and improvement of active skin lesions, but also allowed a good control of the disease over 6 months.

Acknowledgements

This study was sponsored by Novartis Pharma AG. We would like to thank the following investigators who also contributed to the study: PD Dr. R. Lauener, Division of Immunology, Zürich University Hospital, Zürich, Switzerland; Prof. Dr. Theo Rufli, Division of Dermatology, Basel University Hospital, Basel, Switzerland; Prof. Dr. Daniel Hohl, Division of Dermatology, CHUV, Lausanne, Switzerland.

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