

Steroid-Sparing Effect of Pimecrolimus Cream 1% in Children with Severe Atopic Dermatitis

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Key Words

Atopic dermatitis · Eczema · Calcineurin inhibitors

Abstract

Objective: To investigate if pimecrolimus cream 1% reduces the need for steroids in the long-term management of severe pediatric atopic dermatitis (AD). **Methods:** A total of 184 pediatric patients (aged 2–17 years) with a history of severe AD according to Rajka and Langeland were enrolled. Patients were randomized to treatment with pimecrolimus cream or vehicle cream for a 24-week period. Prednicarbate 0.25% was applied as rescue medication. **Results:** Patients on pimecrolimus required steroids on a mean of 29% of study days, compared with 35% of patients on vehicle ($p = 0.1841$). On the head and neck only, the respective figures were 10 versus 19% ($p = 0.0009$). In patients enrolled with acute severe disease (Investigator's Global Assessment ≥ 4), steroids were used on 28% of the days in the pimecrolimus group compared to 45% in the control group ($p = 0.0024$). On the head and neck, steroids were used on 10% of study days

with pimecrolimus versus 30% with vehicle ($p < 0.0001$).

Conclusion: The results indicate that the need for topical steroids on the head and neck is reduced with pimecrolimus cream 1% in the management of severe pediatric AD according to the definition of Rajka and Langeland.

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Introduction

Pimecrolimus has proven effective in the treatment of atopic dermatitis (AD), also known as atopic eczema [1, 2]. Currently pimecrolimus is licensed in the USA and in the European Union countries for treatment of mild to moderate AD in children aged 2 years and above.

The permanent management of chronic AD with topical corticosteroids is associated with safety concerns. As the National Institute for Clinical Excellence, UK, noted, especially patients with moderate and severe AD need active treatment most of the time. With long-term use of topical steroids, this group is at an increased risk of typical steroid side effects like skin atrophy, striae or telangiectasia [3]. Furthermore, systemic side effects of corticosteroids in young children are of particular concern [4]. Steroid-induced skin thinning and telangiectasia occur more readily on the face and neck than elsewhere [5].

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Given the safety issues associated with chronic steroid application in children, the authors conducted this study to determine whether, in children and adolescents with a history of severe AD, the use of pimecrolimus cream from the earliest stages of a developing flare might prevent the exacerbation becoming severe and requiring topical corticosteroid treatment. Pimecrolimus has already shown efficacy in adults with severe AD. In a double-blind randomized study in adult patients with severe AD (Investigator's Global Assessment, IGA = 4) the mean percentage of days on topical corticosteroids during the 6-month treatment period was 23% in the pimecrolimus group ($n = 33$) and 38% ($n = 28$) in the control group ($p = 0.027$) [6].

Methods

Study Design

This was a multicenter, double-blind, randomized, vehicle-controlled, parallel-group study in pediatric patients, 2–17 years of age, with a history of severe AD. The study was approved by the institutional review boards and conducted according to the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, and with the ethical principles laid down in the Declaration of Helsinki. Individual consent was obtained from all patients or their caregivers. A total of 184 patients at 22 dermatological and pediatric centers in Germany were recruited for the study and randomized 1:1, after having controlled the acute flare with prednicarbate cream and provided that all inclusion/exclusion criteria were met, to either pimecrolimus cream 1% or corresponding vehicle cream for at least 7 days in order to control AD.

The main objective was to investigate the corticosteroid-sparing effect of treatment with pimecrolimus cream for up to 24 weeks in the long-term management of severe pediatric AD. Secondary objectives were (i) to investigate if there is superior control of clinical signs when pimecrolimus cream is given in addition to standard therapy with emollients and topical steroids in the long-term management of severe pediatric AD, (ii) to evaluate the safety of pimecrolimus in the long-term management of this patient group and (iii) to assess the patients' and their parents' quality of life.

Patients

Patients were eligible for the study if they were between 2 and 17 years of age and presented with a history of severe AD, as determined by a score of 8 or 9 in the Rajka and Langeland grading [7], and who in case of active symptoms responded within a maximum of 21 days of treatment with prednicarbate cream 0.25% during the screening phase. Within the Rajka and Langeland assessment, each of the following three parameters – extent of disease, duration/course of disease and intensity – are given 1–3 points depending on severity. Unlike the SCORAD, Eczema Area and Severity Index (EASI) or IGA, the Rajka and Langeland score does not evaluate active disease at one time point but reflects the course of the disease. Patients who had received topical steroids within 7 days or phototherapy or systemic corticosteroids/immunosuppressants within 1 month prior to study entry were excluded from the study. Furthermore, children with active acute viral infection or children who were immunocompromised were excluded. Informed consent had been obtained for all patients before inclusion in the study.

Table 1. Baseline demographics and IGA score at screening

	Total ($n = 184$)	Pimecrolimus ($n = 195$)	Vehicle ($n = 89$)
Sex			
Male	89 (48)	43 (45)	46 (52)
Female	95 (52)	52 (55)	43 (48)
Race			
Caucasian	171 (93)	91 (96)	80 (90)
Black	2 (1)	1 (1)	1 (1)
Asian/Oriental	9 (5)	3 (3)	6 (7)
Other	2 (1)	0 (0)	2 (2)
Mean age, years	7.6	8.2	7.0
Standard deviation	4.9	5.1	4.7
Range	2–17	2–17	2–17
<8 years	106 (58)	49 (52)	57 (64)
8–11 years	31 (17)	17 (18)	14 (16)
>11 years	47 (26)	29 (31)	18 (20)
IGA at screening			
0 = clear	0 (0.0)	0 (0.0)	0 (0)
1 = almost clear	6 (3)	1 (1)	5 (6)
2 = mild disease	18 (10)	7 (7)	11 (12)
3 = moderate disease	71 (39)	38 (40)	33 (37)
4 = severe disease	78 (42)	44 (46)	34 (38)
5 = very severe disease	11 (6)	5 (5)	6 (7)
Rajka and Langeland score at screening	8.3	8.3	8.3

Figures in parentheses are percentages.

nosuppressants within 1 month prior to study entry were excluded from the study. Furthermore, children with active acute viral infection or children who were immunocompromised were excluded. Informed consent had been obtained for all patients before inclusion in the study.

Of the 195 screened subjects, 184 were randomized into the trial and exposed to double-blind treatment. Ninety-five subjects were in the pimecrolimus group and 89 in the vehicle group. The baseline demographics and the IGA score at screening were comparable in both treatment groups (table 1). At the time of inclusion into the study, 89 patients presented with severe or very severe acute disease according to the IGA scores, 49 in the treatment group and 40 in the vehicle group.

Treatment

During the screening phase, patients were treated with prednicarbate cream 0.25% for a period of time of at least 7 days (maximal duration = 21 days). If the skin condition did not improve significantly after treatment with prednicarbate 0.25% cream for a maximum of 21 days (as assessed by a marked reduction of itch/scratching and no oozing), the patient was not eligible for the study.

At the baseline visit patients were switched from prednicarbate cream 0.25% to the study medication (plus emollients if needed) for at least 7 days. The treatment with the study medication was applied twice daily as long as signs of AD were present. In case of a flare (unacceptable severity of itching/scratching or onset of

oozing), treatment with prednicarbate cream 0.25% was reinitiated by the patient instead of treatment with the study medication twice per day. As soon as the flare was controlled (marked reduction in itching/scratching and no oozing), the treatment with topical steroids was discontinued and the study medication reinitiated. If all lesions had completely cleared, the patient discontinued the study medication until AD symptoms reappeared. In total, patients received intermittent treatment with the study medication pimecrolimus cream b.i.d. or its vehicle during 24 weeks.

Outcome Measures

The main measure of efficacy was the need for topical steroids during the time between randomization and the end of study measured as the percentage of days on which patients decided to use corticosteroids instead of the study medication. The investigation of disease control by the EASI score, the assessment of safety and the quality of life of the patient and parents were the main secondary endpoints. The EASI is a score between 0 and 72 and is calculated by taking into account the extent and the severity of the clinical signs erythema, infiltration/papulation, excoriation and lichenification [8]. The Patient's Overall Self-Assessment score included pruritus, sleep disturbances and general disease control of the patients. Quality of life was measured at screening, after 6 weeks of treatment and at the end of the study using the Children's Dermatological Life Quality Index [9] and the Parents' Index of Quality of Life-Atopic Dermatitis [10]. The patients/the patient's caregivers reported the days of topical steroid use (i.e. prednicarbate 0.25% cream), days of study medication, any concomitant medication, changes in the patient's medical conditions or adverse events on diary cards. This information and interviews of the patient were the basis for assessment supplementing data obtained at study visits.

Statistical Methods

The double-blind character of the study was preserved by the use of study medication of identical appearance and odor. Randomization was performed by MIPS Novartis Germany using a validated system that automated the random assignment of treatment groups to randomization numbers. Until unblinding, randomization data were kept strictly confidential. At the conclusion of the study, all emergency code-break envelopes were returned to Novartis, and their integrity was checked. All personnel directly involved in the conduct of the study remained blinded to the treatment assignment until all patients had completed the study and all data had been retrieved and finalized for analysis.

The intention-to-treat population was used for the primary efficacy evaluation. The primary endpoint of the study was the percentage of days on rescue medication with prednicarbate cream 0.25%. The probability that an arbitrary patient from the Elidel group would have a better outcome compared to another arbitrary patient from the control group was estimated as being 65%. Under this assumption, 80 patients/group are required to achieve a power of 90% on a significance level of 5% for the 2-sided Wilcoxon test. To compensate for some anticipated protocol violations and/or early dropouts, 90 patients/group should be randomized into this trial.

During a blind data review, it was seen that although the raw data were heavily tailed, the distribution of the (studentized) residuals from the linear model variable – center, age class, baseline affected body area and baseline EASI – looked reasonably normal

to justify a parametric analysis. Since especially the baseline EASI seemed to be highly prognostic, switching to an adjusted parametric analysis promised a higher precision for the estimation of treatment contrasts. Therefore, it was decided to use a parametric ANCOVA model with the factors/covariates center, age class, baseline affected body area and baseline EASI for the analysis of the primary endpoint as well as for the secondary endpoint 'mean postbaseline EASI score'. An additional post-hoc analysis was performed for the subgroup of patients with high IGA scores at screening (4 or 5). This subgroup is especially relevant as the objective of the study was to evaluate pimecrolimus in severe disease. Furthermore, the subgroup of head and neck was analyzed as this body region is especially prone to steroid side effects.

Results

Of the 195 screened subjects, 184 were randomized into the trial and exposed to double-blind treatment with either pimecrolimus 1% twice daily or vehicle. Patients were well balanced regarding baseline and anamnestic data but unexpectedly the Rajka and Langeland score did not correlate closely with active severe disease. Thus only 48% of the whole population had active severe AD at screening (IGA score 4 or 5, table 1).

Pimecrolimus Reduced the Number of Days with Need for Topical Steroids in the Whole Study Group

Evaluating the data of the whole group (IGA 1–5), patients on pimecrolimus required additional steroids on $29 \pm 25\%$ of all study days, compared with $35 \pm 25\%$ for patients on vehicle. Although this indicates a trend in favor of the pimecrolimus group, the difference did not reach statistical significance. The difference between the groups was 6% of the days (95% confidence interval 11.8 to -2.3%, $p = 0.1841$). Prednicarbate was required on significantly fewer days for the treatment of head/neck (10 ± 14 vs. $19 \pm 22\%$, difference 9% of the days, 95% confidence interval 14.1 to 3.7, $p = 0.0009$) in the pimecrolimus group whereas the study did not show a significant difference in the number of days steroids were used on the rest of the body (27 ± 25 vs. $30 \pm 24\%$, $p = 0.64$).

With respect to the secondary endpoints, a positive effect for pimecrolimus that did not reach statistical significance could be demonstrated for the mean EASI score during treatment, which was 7 ± 6 in the pimecrolimus group and 9 ± 8 in the control group ($p = 0.0827$).

Parents' but Not Patients' Quality of Life Significantly Improved

Parents' quality of life as measured by the PIQoL-AD was significantly improved by treatment with pimecrolimus

Table 2. Quality of life assessments

Visit	n	Mean score	SD	p value
<i>Parents' Index of Quality of Life in AD</i>				
Visit 1 (screening)				
Elidel	86	8.3	5.09	0.2406
Vehicle	81	9.3	5.02	
Difference Elidel-vehicle	–	–0.9		
Visit 5 (week 6)				
Elidel	76	5.3	4.77	0.0405
Vehicle	68	7.2	5.78	
Difference Elidel-vehicle	–	–1.8		
Visit 9 (week 24 or study end)				
Elidel	68	4.2	5.17	0.0470
Vehicle	61	6.2	5.93	
Difference Elidel-vehicle	–	–2.0		
<i>Children's Dermatological Life Quality Index</i>				
Visit 1 (screening)				
Elidel	61	9.0	4.93	0.4531
Vehicle	51	9.7	5.40	
Difference Elidel-vehicle	–	–0.7		
Visit 9 (week 24 or study end)				
Elidel	59	3.6	3.65	0.2246
Vehicle	45	4.6	4.57	
Difference Elidel-vehicle	–	–1.0		
Change during study (abs.)				
Elidel	53	5.9	5.52	0.2096
Vehicle	45	4.6	5.30	
Difference Elidel-vehicle	–	1.4		
Change during study, %				
Elidel	53	50.5	64.78	0.7598
Vehicle	44	47.0	44.47	
Difference Elidel-vehicle	–	3.5		

Table 3. Mean EASI score in the treatment group compared to vehicle over the whole study period for subgroup of patients with severe AD according to the IGA score

Variable	n	Mean score	SD	p value
Mean score for itching				
Elidel	49	1.2	0.46	0.0048
Vehicle	40	1.5	0.58	
Difference Elidel-vehicle	–	–0.3		
Mean score for sleep disorder				
Elidel	49	0.8	0.65	0.0091
Vehicle	40	1.1	0.70	
Difference Elidel-vehicle	–	–0.4		
Mean overall assessment				
Elidel	49	2.3	0.68	0.0289
Vehicle	40	2.7	0.86	
Difference Elidel-vehicle	–	–0.4		

mus cream as compared with the control group after acute and after long-term treatment, whereas the improvement in quality of life of the patients was similar in the pimecrolimus group and in the control group with standard therapy and vehicle (table 2).

In Patients with Severe and Very Severe AD at Enrollment Pimecrolimus Reduced the Number of Days Corticosteroids Were Used and Improved Disease Control

In the subgroup of study patients with active severe AD (IGA 4 or 5) which was analyzed post hoc after unblinding, pimecrolimus significantly reduced the percentage of days with steroid application and the mean EASI score. In the course of the 24-week study topical steroid was used on a mean of $28 \pm 21\%$ of days in the pimecrolimus group as compared to $45 \pm 27\%$ in the control group. The difference between the groups was 17% of the days (95% confidence interval 24.8 to 5.6%, $p = 0.0024$). The mean EASI score was 9 ± 7 in the pimecrolimus group and 13 ± 10 in the vehicle control group ($p = 0.0041$). Subjective symptoms like itch and sleep disorders as well as the patients' overall assessment were significantly better in the pimecrolimus group (table 3) than in vehicle-treated patients. Pimecrolimus cream was especially effective when used on the head and neck where topical steroids needed to be applied only on $10 \pm 15\%$ of the study days versus $30 \pm 27\%$ in the control group (difference 20% of the days, 95% confidence interval 29.5 to 11.1%, $p < 0.0001$).

Safety

Adverse events occurred in 86% of the patients in the pimecrolimus group and in 85% of those in the vehicle group. The vast majority of the adverse events were infections of the respiratory tract, typical among children. Only 5 adverse events with suspected drug relationship occurred in 5 patients of the pimecrolimus group, compared with 10 such events in 4 patients of the vehicle group. In the pimecrolimus-treated patients the drug-related adverse events were application site burning ($n = 2$), herpes simplex ($n = 1$), impetigo ($n = 1$) and molluscum contagiosum ($n = 1$). In the vehicle group, 1 patient had 6 allergic eye disorders such a keratitis, blepharitis and conjunctivitis. One patient experienced application site burning. The other adverse events were herpes virus infection ($n = 1$), impetigo ($n = 1$) and contact dermatitis ($n = 1$). There was no sign of any relevant change in hematological or biochemical laboratory parameters.

Twenty-nine subjects discontinued the trial prematurely. The discontinuation rate was almost twice as high with vehicle as with pimecrolimus (20 vs. 12%). The primary reason for the discontinuation of these patients was an 'unsatisfactory therapeutic effect'.

Discussion

AD is a chronic or chronic relapsing skin disease which often requires daily treatment over extended periods. Successful long-term management of the condition should not only improve the patient's disease state, but also decrease the amount and/or frequency of treatment needed to maintain control of AD [11]. Pimecrolimus has shown efficacy in AD in various clinical studies [2, 12]. The severity of the AD has been assessed in different ways including the SCORAD index [13], EASI [8], IGA, the Six Symptoms and Severity Score in AD [14] and the Rajka and Langeland score [7]. In contrast to the other scores which measure the current clinical severity of AD, the Rajka and Langeland score considers the course/duration of the disease – a measure that should be included according to some European authorities – when grading disease severity. Although the study was initiated to investigate patients with severe AD, some investigators and one study center in particular included patients with only high scores according to Rajka and Langeland but very low active disease according to IGA scores which may represent patients in between flares. Post hoc, this phenomenon was largely explained by the fact that these investigators took into account the symptom 'dryness of the skin' when assessing the extent of disease and the days with active disease within the last year.

Both exclusion of the one study center which had enrolled most of the patients with mild (IGA = 2) or very mild (IGA = 1) disease and the exclusion of all patients with baseline IGA lower than 3 (moderate disease – results not shown) or 4 (severe disease) resulted in a significant difference in the primary parameter 'days on topical corticosteroids'. Analysis of the subgroup of severe AD patients according to both scores, the Rajka and Langeland score and the IGA showed that in this subgroup topical steroid was used during the 24-week study period on a mean of 28% of the days in the pimecrolimus group as compared to 45% in the control group ($p = 0.0024$). The difference of 17% is almost identical with the results from adult patients ($n = 61$) with severe AD (IGA = 4) where during a 24-week study period topical steroids were used on 23% of the days in the pimecrolimus

group as compared to 38% in the control group ($p = 0.027$) [6].

The results for the whole study population showed still a clear significance between pimecrolimus and vehicle in reducing the number of days on which steroids were used when looking on the head and neck area only. In general, the study has demonstrated a steroid-sparing effect of pimecrolimus versus vehicle and bland emollients which by themselves reduce the need for topical steroids as published in a recent study [15].

The results on the parents' quality of life in this study are very similar to an earlier study in children with mild to very severe AD [16]. However, the effect on the children's life quality is different in the two studies: In our trial there was a much stronger improvement in quality of life which could in contrast to the earlier trial also be found in the control group. There is no clear explanation for this; however, it is conceivable that children in the control group in contrast to their parents had already such a good quality of life with standard therapy in this study that addition of pimecrolimus could not lead to a substantially better benefit.

Although more than 80% of the patients in each treatment group experienced adverse events, only 5 patients treated with pimecrolimus (5.3%) and 4 patients in the vehicle group (4.5%) had adverse events with a suspected drug relationship. Five adverse events occurred in the pimecrolimus group and 10 in the vehicle group. The incidence of application site burning was very low in the study occurring in only 2 patients in the pimecrolimus group and 1 patient in the control group. Overall our data are in line with observations from other studies that children respond well to pimecrolimus and report only few side effects like skin burning [17].

In conclusion, the study demonstrated a steroid-sparing effect of pimecrolimus cream 1% on the head and neck in AD patients with severe disease according to the definition of Rajka and Langeland.

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