

Treatment of infants with atopic eczema with pimecrolimus cream 1% improves parents' quality of life: A multicenter, randomized trial

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Atopic eczema begins primarily in infancy or early childhood, and sleep loss due to night-time pruritus can have a considerable impact on patients' and parents' quality of life (QoL). In this study, infants ($n = 196$) with mild to severe atopic eczema were randomized 2:1, double-blind, to receive either pimecrolimus cream 1% (Elidel®, Novartis Pharma, Nürnberg, Germany) or the corresponding vehicle bid for 4 wk, followed by a 12 wk, open-label phase and a 4 wk, treatment-free, follow-up period. The parents' QoL was measured at baseline and at the end of the double-blind phase, using the questionnaire 'QoL in Parents of Children with Atopic Dermatitis' (PQoL-AD), thus data presented here refer to the initial 4-wk treatment phase only. After 4 wk of double-blind treatment, an increase in the mean percentage change from baseline in eczema area and severity index of 71.5% was observed with pimecrolimus, compared with 19.4% with vehicle. The increase in efficacy was paralleled by the following mean percentage changes from baseline in the five domains of the questionnaire in pimecrolimus and vehicle, respectively: psychosomatic well-being: 14.6% vs. 6.2%; effects on social life: 6.7% vs. 2.3%; confidence in medical treatment: 10.0% vs. 3.7%; emotional coping: 16.1% vs. 6.5%; acceptance of disease: 19.6% vs. 7.0%. Analysis (ANCOVA) of the dependent variable difference from baseline and the covariate baseline value revealed values of $p < 0.05$ for all five domains, despite the very short duration of the study. It is concluded that improvements in atopic eczema in infants achieved by treatment with pimecrolimus have a significant beneficial effect on the QoL of parents.

**Doris Staab¹, Roland Kaufmann²,
Matthias Bräutigam³, Ulrich Wahn⁴
and the CASM981CDE04-Study Group**

¹Charité-Virchow Klinikum, Kinderklinik und Poliklinik, Berlin, Germany, ²Johann Wolfgang Goethe-Universität, Hautklinik, Frankfurt am Main, Germany, ³Novartis Pharma GmbH, Clinical Research, Nürnberg, Germany, ⁴Charité Campus Virchow, Berlin, Germany

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Doris Staab, Department of Paediatric Pulmonology and Immunology, Charité, Humboldt-University, Helios-Klinikum Emil von Behring, Zum Heckeshorn 30, 14109 Berlin, Germany
Tel.: +49 30 8102 2205
Fax: +49 30 8102 2278
E-mail: doris.staab@charite.de

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Atopic eczema is characterized by dry and itchy skin, with frequent relapses of inflammation and extreme pruritus. The vicious cycle of itching and scratching leads to restlessness of the child and, usually, disturbed sleep for the whole family. Since parental stress and negative emotions have been proven to aggravate a child's symptoms (1), it seems important to examine the effects on the family system in the evaluation of new therapies.

Atopic eczema has been shown to affect children's physical abilities, emotions and behavior, social skills, self-esteem and overall psychological development (2, 3). The condition has

also been shown to have a profound impact on the emotional and social well-being of many parents (4), who are more likely to feel distressed, tired and exasperated than parents with unaffected children, and to be troubled by child behavioral problems (5). Chronic pruritus, skin infections, lack of sleep, lowered self-esteem, and growth and developmental problems can be debilitating for both the child and the family (6). Family members may also experience sleep deprivation and are subjected to limitations in lifestyle, altered social and holiday plans, and adverse effects on relationships (7).

It has been demonstrated that there is a correlation between atopic eczema disease severity and the quality of life (QoL) of patients and their families (8–10).

Pimecrolimus is a non-steroid, inflammatory-cytokine inhibitor, formulated as a 1% cream (Elidel®) for the treatment of atopic eczema (11). Pimecrolimus works by selectively inhibiting the expression of inflammatory cytokines by inflammatory T cells and preventing the release of pro-inflammatory mediators by mast cells (12–14). Prevention of flares, relief of pruritus and effective long-term control of atopic eczema has been demonstrated in several large, multicenter, controlled studies with pimecrolimus cream 1% (15–17).

Here, we present the results of a multicenter, vehicle-controlled study of the QoL benefits, efficacy and safety of pimecrolimus in infants with mild to very severe atopic eczema.

Methods

Study design

This was a 20 wk, randomized, controlled, multicenter study, comprising three phases. The first was a double-blind, vehicle-controlled, parallel-group phase, during which patients were randomly assigned 2:1 to receive either pimecrolimus or the vehicle equivalent for 4 wk. This phase was followed by a 12 wk, open-label extension phase, during which all patients received pimecrolimus. Patients could be switched to open-label pimecrolimus treatment after 2 wk of the double-blind phase if they achieved total disease clearance or if they did not show any improvement. The third phase was a 4-wk follow-up, in which active treatment was discontinued in all patients, to enable the return of symptoms to be assessed. The study design was approved by the participating hospitals' Institutional Review Boards, and was conducted according to the Declaration of Helsinki and the standards of Good Clinical Practice (18).

Data presented here refer only to the initial double-blind phase. Results of the open-label and follow-up phases are reported elsewhere (19).

Patients

The study was conducted in pediatric patients aged 3–23 months, with a diagnosis of atopic eczema (20) affecting $\geq 5\%$ of the body surface area and with a baseline Investigators' Global Assessment (IGA) score of 2 (mild disease severity) or greater, based on the degree of erythema

and infiltration/population. Eligible patients also had atopic eczema affecting the face. Patients with insufficient wash-out periods – i.e., ≤ 1 month for systemic corticosteroids and phototherapy, < 2 wk for antibiotics and < 1 wk for topical steroids or other topical therapies that might have an effect on atopic eczema – were excluded. Other excluded groups were immunocompromised patients, patients with other significant concomitant diseases or those with a known hypersensitivity to the study drug. Written, informed consent by the patient's legal guardian was required. The study was conducted between June 2001 and July 2002 at 19 centers in Germany.

Treatment

Primary caregivers were instructed to apply pimecrolimus, or the corresponding vehicle equivalent, to the patient twice-daily during the double-blind phase. Applications were made approximately 12 h apart (typically 08.00 and 20.00), as a thin film on all areas affected by atopic eczema. The first application was made at the study center, under the supervision of an investigator or nurse, to ensure that the correct procedure was followed. During the 4-wk double-blind phase, emollients were only permitted on areas not treated with study medication.

Assessments

The parents' QoL was measured at baseline and at the end of the 4-wk double-blind treatment phase, using the questionnaire 'QoL in Parents of Children with Atopic Dermatitis' (PQoL-AD), which was completed by the parents/primary caregivers. This questionnaire should not be confused with a similar one, the 'Parents' Index of QoL-Atopic Dermatitis' (PIQoL-AD), developed by McKenna et al. (21). It consists of 26 items, which can be divided into five subscales: psychosomatic well-being; effects on social life; confidence in medical treatment; emotional coping; and acceptance of the disease (22). Positively and negatively formulated items were answered on a 5-point Likert scale ranging from 1 (completely disagree) to 5 (completely agree). Negative items were re-coded before analysis so that high values corresponded to a high QoL rating.

Pruritus and sleep loss in infants were assessed by the primary caregiver using a visual analog scale ranging from 0 to 10, as specified in the Severity Scoring of Atopic Dermatitis (SCOR-AD) assessment tool for atopic eczema (23, 24). The intensity of overall itching/scratching and the sleep loss of the subject in the 3 days

Table 1. The SCORAD index

Objective SCORAD

The objective SCORAD provides a score of the extent and intensity of atopic eczema, and is a composite index that ranges from 0 to 83 (23, 28).

The extent of atopic eczema was evaluated by applying the rule of nines (0–100%). The intensity of atopic eczema was scored using a 4-point scale from 0 (absent) to 3 (severe disease)

The following criteria were evaluated by this score: erythema; edema/papulation; oozing/crusting; excoriation; lichenification; dryness.

The maximum possible total SCORAD value for all six criteria is 18.

The assessment scores for the extent and intensity of eczema were incorporated to produce an 'objective' SCORAD, using the following formula: $\text{objectiveSCORAD} = (\text{extent}/5) + (3.5 \times \text{intensity})$

Severity of pruritus and sleep loss

Overall pruritus and sleep loss were assessed individually using a visual analog scale ranging from 0 to 10. Therefore, the maximum possible total value for 'severity of pruritus and sleep loss' was 20. Pruritus and sleep loss were evaluated by the primary caregiver, who assessed the intensity of overall itching/scratching and amount of sleep loss of the patient in the 3 days and nights prior to the study visit (until Day 8, the values related to the day and night prior to the visit)

With these subjective values, it was possible to calculate the SCORAD Index (totaling 0–103 for the three criteria) by adding the values for severity of pruritus and sleep loss to the objective SCORAD.

$\text{SCORAD index} = \text{objective SCORAD} + \text{severity of pruritus} + \text{severity of sleep loss}$

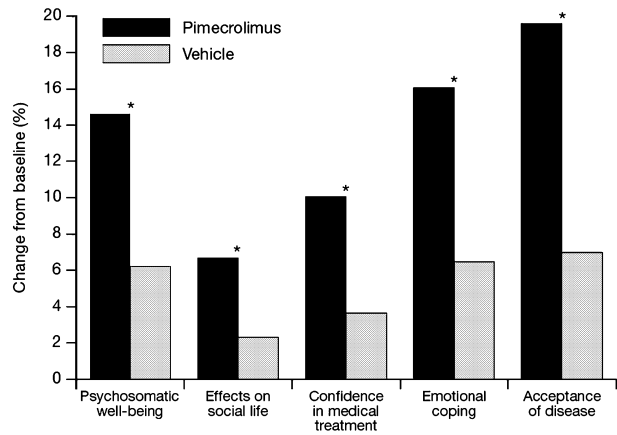
and nights prior to the visit were reported. Furthermore, the severity of eczema was examined with the SCORAD Index, a score combining subjective and objective parameters of disease activity – the objective SCORAD, pruritus and sleep loss (Table 1).

The severity of disease was also assessed using the IGA, a 6-point scale from 0 (clear) to 5 (very severe disease) (15). This scale measures disease severity based on morphology, without reference to the baseline state. The IGA also enabled the proportion of patients with a flare, defined by an IGA score of 4 or 5 (severe or very severe disease), to be determined at each assessment.

The patient's primary caregiver was asked to assess the degree of disease control over the previous 7 days, using a 4-point scale from 0 (complete disease control) to 3 (uncontrolled disease). The Eczema Area and Severity Index (EASI) was used to assess erythema, infiltration/papulation, excoriation and lichenification separately, in the head and neck region, trunk, upper limbs and lower limbs. Proportionate values are assigned to each of these four body regions, and Figs 1 and 2 are combined to yield an overall EASI ranging from 0 (no disease present) to 72 (all signs of disease rated severe and present over 100% of the body surface).

Blinding and statistical analysis

Patients were assigned to treatment according to a computer-generated, blinded randomization list.



* $p < 0.05$

Fig. 1. Mean percentage change in parents' index of QoL from baseline to Day 29.

The double-blind status of the initial phase of the study was maintained by the use of study medication and vehicle of identical appearance and odor. Efficacy was analyzed in the intention-to-treat (ITT) population using the last observation carried forward method for patients who discontinued participation. Differences in changes in EASI and SCORAD between the pimecrolimus cream 1% and vehicle control treatment groups were compared by an adjusted analysis of covariance (ANCOVA); for comparisons of IGA scores the Cochran–Mantel–Haenszel-test was applied.

The subject's assessment of pruritus and sleep loss on a 0–10 analog scale was analyzed throughout and at endpoint (double-blind phase), and presented as sample statistics by treatment group over time. The baseline for changes in pruritus and sleep loss was the last day before commencing treatment with study medication.

QoL at the beginning of and after the end of the double-blind phase was analyzed using sample statistics. Before analysis, the items of the QoL index were summarized after re-coding negative items, so that high values corresponded to high QoL. For the changes of clinical scores (EASI, IGA and SCORAD) and of domains of life quality from baseline to Week 4, correlation coefficients by Pearson were calculated.

Results

Patients

In total, 201 patients were included in the study at 19 centers; 196 of these patients were allocated to randomized treatment, 130 with pimecrolimus and 66 with vehicle. A total of 13 patients (10%) in the pimecrolimus group and 25 patients (37.9%) in the vehicle group discontinued

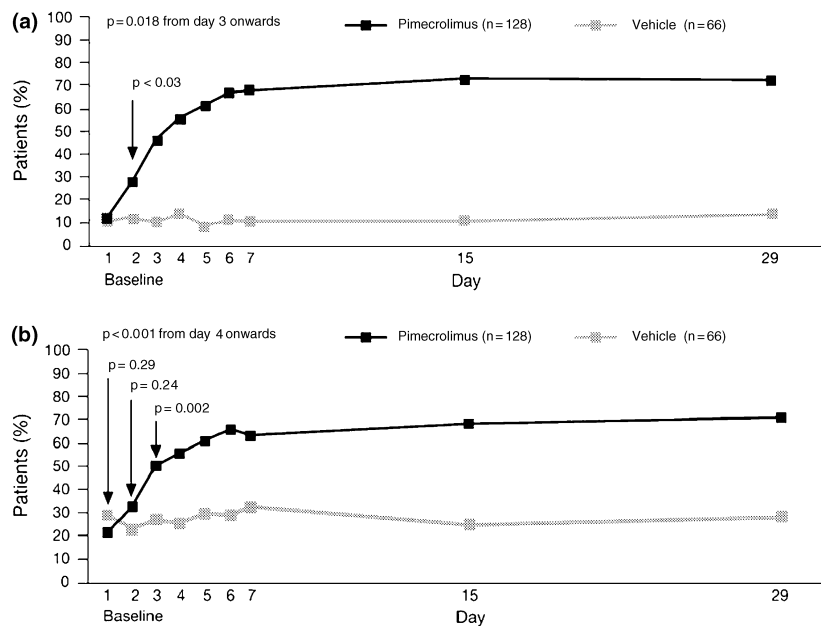


Fig. 2. Percentage of patients with an improvement of at least 50% from baseline according to the primary caregiver's assessment (visual analog scale). (a) Pruritus; (b) sleep loss.

double-blind treatment before completion of the full 4 wk. The main reason for early discontinuation was lack of therapeutic effect in five patients (3.8%) in the pimecrolimus group and 23 patients (34.8%) in the vehicle group.

The baseline demographic and clinical characteristics of the ITT population are shown in Table 2. There was no significant difference in age and disease severity between the two groups.

Signs and symptoms

Pimecrolimus was effective and fast-acting in reducing the signs and symptoms of atopic

eczema during the double-blind phase. A statistically significant pruritus treatment effect (percentage of patients with an improvement of at least 50% from baseline) in favor of pimecrolimus was noted by Day 2 (27.3% vs. 12.1%, $p = 0.018$), and a significant improvement in sleep loss by Day 3 (49.2% vs. 25.8%, $p = 0.002$) (Fig. 2). By Day 29, the mean percentage change from baseline in SCORAD Index was -55.2% for the pimecrolimus group and $+1.13\%$ for the vehicle group ($p = 0.002$).

Treatment success [IGA = 0 (clear) or IGA = 1 (almost clear)] was achieved in 53.5% of the pimecrolimus group at Day 29, compared with 10.6% of patients in the vehicle group ($p < 0.001$). Improvements were also observed in the measurement of EASI, where the mean EASI fell by 71.5% in the pimecrolimus group, but increased by 19.4% in the vehicle group ($p < 0.001$) at the end of Week 4. The response to pimecrolimus treatment was rapid, with a reduction of 38.5% in mean EASI by Day 4 (the first 'on-treatment' visit), compared with an increase of 17.6% in the vehicle group ($p < 0.001$).

Quality of life

After 4 wk of double-blind treatment, significant improvements in favor of pimecrolimus were seen by parents in all five domains of the PQoL-AD (Fig. 1 and Table 3) (ANCOVA, $p < 0.05$). The most notable differences were observed in the mean percentage change from baseline in 'psychosomatic well-being' (14.61% change from baseline in the pimecrolimus group vs. 6.22% for

Table 2. Baseline demographics and disease characteristics

	Pimecrolimus (n = 129)	Vehicle (n = 66)
Age, months (mean $\pm$ s.d.)	12.3 $\pm$ 6.1	11.5 $\pm$ 5.8
Gender [n (%)]		
Male	81 (62.8)	47 (71.2)
Female	48 (37.2)	19 (28.8)
Ethnicity [n (%)]		
Caucasian	117 (90.7)	61 (92.4)
Black	2 (1.6)	0 (0)
Asian	7 (5.4)	4 (6.1)
Other	3 (2.3)	1 (1.5)
Height, cm (mean $\pm$ s.d.)	75.3 $\pm$ 8.0	74.4 $\pm$ 7.2
Weight, kg (mean $\pm$ s.d.)	9.4 $\pm$ 2.1	9.4 $\pm$ 2.0
IGA score [n (%)]		
2 (Mild)	12 (9.3)	8 (12.1)
3 (Moderate)	75 (58.1)	39 (59.1)
4 (Severe)	34 (26.4)	17 (25.8)
5 (Very severe disease)	8 (6.2)	2 (3.0)
EASI (mean $\pm$ s.d.)	17.7 $\pm$ 10.8	16.6 $\pm$ 10.3
SCORAD index (mean $\pm$ s.d.)	48.6 $\pm$ 15.0	46.9 $\pm$ 15.9

EASI, eczema area and severity index; IGA, investigators' global assessment; s.d., standard deviation

Table 3. Parents' index of QoL

Parameter	Pimecrolimus (n = 129), Mean (range)	Vehicle (n = 66), Mean (range)
Psychosomatic well-being		
Day 1	3.3 (1.3–5.0)	3.3 (1.1–5.0)
Day 29	3.6 (1.4–5.0)	3.4 (1.0–4.9)
Effects on social life		
Day 1	3.9 (1.7–5.0)	3.9 (1.0–5.0)
Day 29	4.1 (2.0–5.0)	3.9 (1.2–5.0)
Confidence in medical treatment		
Day 1	3.9 (1.8–5.0)	3.9 (2.2–5.0)
Day 29	4.2 (2.0–5.0)	4.0 (2.2–5.0)
Emotional coping		
Day 1	3.4 (1.0–5.0)	3.4 (1.3–5.0)
Day 29	3.8 (1.8–5.0)	3.5 (1.3–5.0)
Acceptance of disease		
Day 1	3.6 (1.0–5.0)	3.6 (1.0–5.0)
Day 29	3.9 (1.0–5.0)	3.7 (1.0–5.0)

Table 4. Correlation between changes in clinical efficacy parameters and in parents' QoL (ITT population)

	Parents' index of QoL				
	QOL-P *	QOL-S *	QOL-C *	QOL-E *	QOL-A *
Visit 2 (Day 1, Week 1)					
SCORAD	–0.484	–0.400	–0.169	–0.319	–0.218
IGA	–0.224	–0.207	–0.005	–0.209	–0.137
EASI	–0.277	–0.260	–0.118	–0.256	–0.077
Visit 6 (Day 29, Week 5)					
SCORAD	–0.394	–0.404	–0.301	–0.323	–0.246
IGA	–0.279	–0.237	–0.267	–0.259	–0.264
EASI	–0.249	–0.249	–0.225	–0.197	–0.183

*Parents' index of QoL: QOL-P, psychosomatic well-being; QOL-S, effects on social life; QOL-C, confidence in medical treatment; QOL-E, emotional coping; QOL-A, acceptance of the disease

vehicle), 'emotional coping' (16.06% vs. 6.48%, respectively) and 'acceptance of disease' (19.58% vs. 6.98%, respectively). Analysis of the relationship between clinical parameters and QoL showed only weak correlations (Table 4).

Safety

Local tolerability of pimecrolimus was excellent. Parents' reports of application-site burning were rare, occurring in only one patient in each group. There were no clinically significant differences between the groups in the occurrence of any skin infections or infestations.

Discussion

Atopic eczema has been shown to adversely affect the well-being of both patients and their parents, and can exert a traumatizing effect on family life (2–7). A correlation has been shown

between the severity of atopic eczema and the QoL of patients and their families (8, 9). Sleep loss due to pruritus is known to be particularly common when a child is experiencing a flare of atopic eczema (25), and can be very debilitating – repeated excoriations and skin trauma caused by scratching can lead to *Staphylococcus aureus* colonization and chronic skin changes, while sleep disturbance can have an adverse impact on the patient's family. Rapid alleviation of pruritus combined with improvements in disease signs may have significant effects on the QoL of both the child and the caregiver.

The PQoL-AD questionnaire is particularly suited to this very young population (aged 3–23 months), as it allows the impact of atopic eczema to be assessed from the first few months of a child's life, by evaluating the impact of disease symptoms and functioning on the parents' QoL. The questionnaire contrasts with other measures, such as the Children's Dermatology QoL Index (26, 27), which focuses on the direct symptomatic and functional impact of the condition and can, consequently, only be used in older children.

In this study, pimecrolimus was effective in the treatment of atopic eczema in infants. The rate of improvement in terms of pruritus and patients' sleep loss, as assessed by caregivers, was very rapid. Statistically, significant differences between the pimecrolimus and vehicle groups, in the percentage of patients with at least a 50% improvement from baseline, were observed as early as Day 2 for pruritus and Day 3 for sleep loss. The full effects of treatment were predominantly achieved within 1 wk, and sustained thereafter. When these values were combined as part of the SCORAD Index, it was shown that pimecrolimus produced a significant improvement in parents' condition, compared with vehicle.

This clinical efficacy manifested itself in significant improvements in all domains of the PQoL-AD questionnaire observed during 4 wk treatment, encompassing psychosomatic well-being, effects on social life, confidence in medical treatment, emotional coping and acceptance of disease.

Consistent with other studies, this trial showed only weak correlations between clinical parameters and QoL. This suggests that patients' clinical scores do not sufficiently describe the improvement in parent's QoL, and that measurement of QoL is an important complementary assessment to the clinical evaluation. Since clinical symptoms and functioning are mediators of QoL, there may be a time delay before the full impact

of improvements in disease can be measured, in terms of the QoL factors. The maximum benefit to parents' QoL derived from treatment may not have been evident in this study as the investigational period was relatively short (4 wk). Further investigation to assess the long-term QoL benefits from treatment is advisable.

In conclusion, treatment with pimecrolimus has a beneficial effect on disease signs and symptoms and, consequently, infants' sleep loss, which should improve the QoL of the parents. The treatment response is rapid, with clinically significant improvements in pruritus and other clinical signs of atopic eczema evident within 48 and 72 h, respectively, compared with vehicle treatment responses. Sleep loss is also rapidly improved. These findings suggest that the treatment of atopic eczema using pimecrolimus is an important advance toward improving the QoL of parents coping with infants with atopic eczema.

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