

## Original article

# Onset of pruritus relief with pimecrolimus cream 1% in adult patients with atopic dermatitis: a randomized trial

**Background:** Pimecrolimus cream 1% (Elidel, Novartis Pharmaceuticals AG) effectively improves/relieves pruritus associated with atopic dermatitis (AD), but few data are available regarding the timing of relief. The purpose of this study was to investigate the timing of pruritus relief produced with pimecrolimus in adults with mild/moderate AD and moderate/severe pruritus.

**Methods:** Patients were randomized to 7 days of treatment with pimecrolimus ( $n = 100$ ) or vehicle ( $n = 98$ ). Pruritus severity was assessed daily on a 4-point scale (0 = absent, 3 = severe), reflecting the previous 24 h experience. Patients who completed this core study were eligible to enter a voluntary 5-week, open-label extension study.

**Results:** A significant effect was noted within 48 h of treatment, with pruritus improving in 56% of pimecrolimus-treated patients and 34% of vehicle-treated patients ( $P = 0.003$ ). Pruritus relief was maintained during the remainder of the core and extension phases, and was accompanied by an improvement in the Investigator's Global Assessment score.

**Conclusion:** Pimecrolimus cream 1% significantly reduced pruritus within 48 h.

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Pruritus is often cited as the most 'bothersome' aspect of atopic dermatitis (AD) and is one of the first symptoms of an impending AD flare (1). Atopic dermatitis is often referred to as the 'itch' that 'rashes' (2); patients scratch the pruritic areas of skin, which aggravates skin inflammation. Thus, treatment that rapidly alleviates pruritus could be considered a major goal in AD management.

The pathophysiology of pruritus associated with AD is complex (3). Cutaneous nerves are affected at the areas of actively inflamed atopic skin; levels of several neuropeptides are altered in lesional vs unaffected skin (4, 5). In addition, pruritus is potentially mediated by inflammatory cytokines, such as IL-2 (6).

Early studies suggested that pruritus in AD was partially due to mast cell release of histamine. However, evidence for the effectiveness of antihistamines in relieving AD-associated pruritus is limited, and the magnitude of effect appears to be minimal (7, 8).

Pharmacological and non-pharmacological strategies are used clinically to control AD-associated pruritus, illustrating the probable multifactorial aetiology of pruritus (9). Emollients are used to treat dry skin along with nonimmunomodulatory agents aimed at pruritus relief, e.g. oral antihistamines (8) and tricyclic antidepressants (10, 11). These are used for their sedative effects, to supplement or precede treatment of active inflammation with immunomodulating agents.

There are currently limited published data regarding the speed of pruritus relief following the use of immunomodulatory agents. Pimecrolimus is a nonsteroid, selective inhibitor of the production and release of inflammatory cytokines in T cells, and of other proinflammatory mediators in mast cells (12–16). Previous studies have shown that pimecrolimus cream 1% is effective in resolving the signs and symptoms of AD and has a favourable safety profile (17–21). However, few data are available regarding the timing of the onset of relief.

The present study investigates the speed of pruritus relief in adults with long-standing AD treated with pimecrolimus cream 1% over a 7-day period.

Patients and methods

Study design

This was a randomized, double-blind (DB), parallel-group, vehicle-controlled study conducted at 25 centres: Germany [12], Denmark [4], Canada [3], Finland [3] and Norway [3]. A total of 198 patients were randomized 1 : 1 to treatment with pimecrolimus cream 1% bid (*n* = 100) or vehicle bid (*n* = 98) (Fig. 1). Randomization was performed using a validated system that automated the assignment of treatment groups.

Patients who completed this core study were eligible to enter a voluntary 5-week, open-label (OL) extension study. This manuscript focuses primarily on the 7-day, DB phase, and briefly summarizes efficacy and safety data from the 5-week extension.

Patients

The study population consisted of patients aged 18–81 years with mild–moderate AD (Investigator’s Global Assessment (22) [IGA] 2 or 3) affecting ≥5% of the total body surface area, the majority (84% [167/198]) of whom had moderate–severe pruritus (pruritus score of 2 or 3). The IGA provides an overall static evaluation of disease state on a 6-point scale ranging from 0 (clear: no inflammatory signs of AD) to 5 (very severe disease: severe erythema and severe papulation/infiltration with oozing/crusting). Pruritus severity was assessed using a 4-point scale: 0: absence of pruritus; 1: mild pruritus (occasional slight itching/scratching); 2: moderate pruritus (constant or intermittent itching/scratching that does not disturb sleep) and 3: severe pruritus (bothersome itching/scratching that disturbs sleep).

Statistical analysis was performed on four patient populations: randomized, safety, intent-to-treat (ITT) and pruritus ITT populations, as described fully in the Statistical analysis section.

All patients were treated with bland emollient for 3 days prior to randomization.

Patients were excluded from the study if they had received any of the following prior to study commencement: topical medication for pruritus relief or antibiotic therapy, within 7 days; systemic medication known to have a sedative effect or to affect pruritus, within 2 weeks; tacrolimus ointment 0.03% or pimecrolimus cream 1%, within 2 weeks; or phototherapy or any systemic therapy known or suspected to have an effect on AD, within 1 month. Patients were also ineligible if they had: concurrent skin disease; AD triggered by an unavoidable irritant/allergen; active infection requiring prohibited treatment; tinea corporis, intertriginous tinea, head lice, scabies, chicken pox or impetigo; or history of poor response to topical tacrolimus ointment. Immunocompromised patients, patients with a history of malignant disease, and females who were pregnant, breast-feeding or not using a medically approved method of contraception were also excluded.

All patients provided written informed consent before entering the study, and the protocol was approved by the Institutional Review Board or Ethics Committee at each participating centre.

Treatment

Study medication (pimecrolimus cream 1% or vehicle) was applied bid to all AD affected areas for seven consecutive days, and concomitant use of bland emollients was permitted in both treatment groups. No systemic or topical therapy (other than

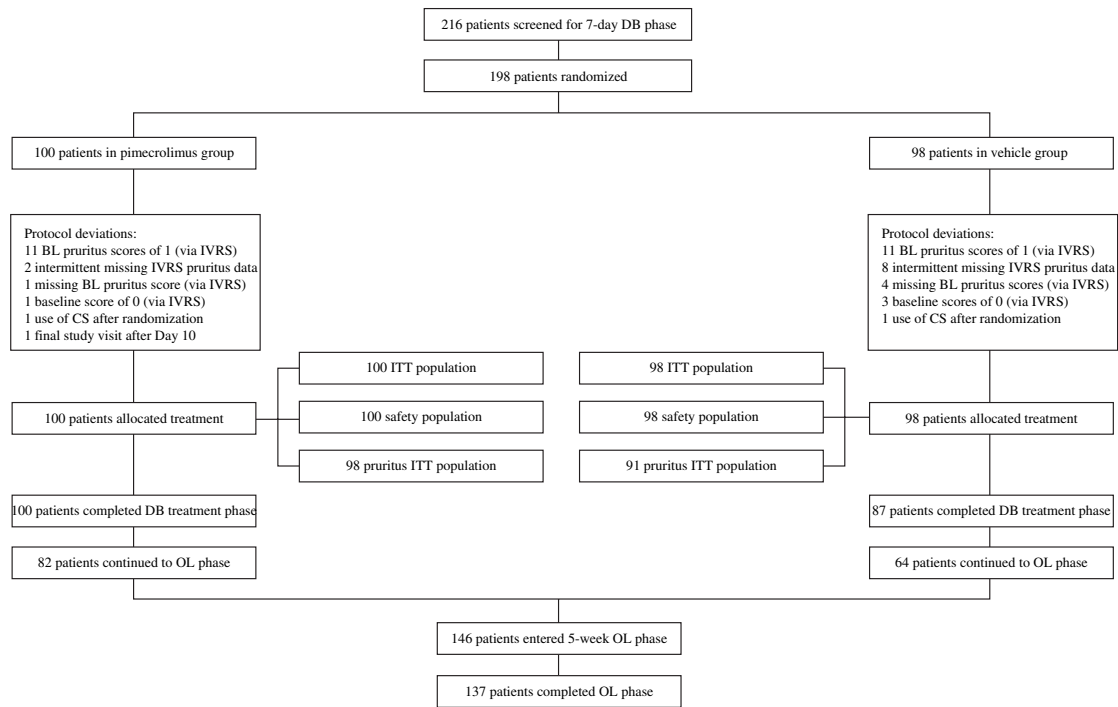


Figure 1. Trial profile. Intention to treat (ITT) population, all randomized patients who received ≥ one dose of study medication; Safety population, all randomized patients who received ≥ one dose of study medication; Pruritus ITT population, all randomized patients who received ≥ one dose of study medication, had a baseline (BL) pruritus score (via Interactive Voice Recognition System [IVRS]) of 1, 2 or 3 and had at least one post-BL efficacy assessment. DB, double-blind; CS, corticosteroid; OL, open label.

study medication) or inhaled corticosteroids at dosages > 1000 b.d.p. µg/day (asthma treatment) were allowed during the treatment period.

### Efficacy evaluations

**Pruritus.** After randomization and prior to the first application of study medication, patients reported baseline pruritus severity scores for the previous 24-h period, via telephone using an Interactive Voice Recognition System (IVRS). At baseline, patients were required to have moderate–severe pruritus (score of 2 or 3). Patients continued to report pruritus scores (overall pruritus severity experienced during the previous 24 h) daily via IVRS (reported at approximately the same time each morning – 7:00 and 12:00 hours). Patients in the 5-week extension also reported pruritus scores at the end-of-study visit. The last 7-day, DB pruritus score was deemed to be the baseline pruritus score of the 5-week extension.

**Investigators' Global Assessment.** Assessments were conducted at baseline, and following completion of 7 days' treatment (day 8). For the 5-week extension, IGA assessments were determined at the end-of-study visit. The last 7-day, DB IGA score was deemed to be the extension baseline IGA score.

The primary efficacy variable was the time taken to achieve pruritus improvement of ≥1 point on a 4-point pruritus severity scale, compared with baseline. The main secondary efficacy variable was the percentage of patients achieving pruritus improvement of ≥1 point compared with baseline (pruritus response), within 48 and/or 72 h. Other secondary efficacy variables included the percentage of patients with a pruritus response within 4, 5, 6 and 7 days' treatment; the percentage of patients with a pruritus severity score of 0 or 1 for treatment days 2, 3, 4, 5, 6 and 7, regardless of baseline scores; and the percentage of patients with an IGA score improvement of ≥1 point at study completion (the end of the DB phase), compared with baseline.

### Safety evaluations

All adverse events (AEs) were monitored and recorded, detailing the severity and relationship to the study drug. Vital signs and standard laboratory data were not collected in this study.

### Statistical analysis

Four patient populations were prespecified as follows: randomized population – all patients who received a randomization number; safety population – all randomized patients who used at least one dose of study medication; ITT population – all safety patients with at least one post-baseline efficacy assessment and pruritus ITT population – all ITT patients with baseline pruritus scores (via IVRS) of 1, 2, or 3.

At the end of the DB phase, the randomized, safety and ITT populations were equivalent in size: 100 patients in the pimecrolimus group vs 98 patients in the vehicle group. The pruritus ITT population comprised those patients with a baseline pruritus score (reported via IVRS) of 1, 2 or 3: 98 patients in the pimecrolimus group (one patient with a missing baseline score, and one with a score of 0 were excluded) vs 91 in the vehicle group (four patients with missing baseline scores and three with a score of 0 were excluded) [Fig. 1, Table 1].

Demographic and baseline disease characteristics were summarized for all randomized patients. Primary and main secondary efficacy analyses were performed using the pruritus ITT population.

Table 1. Baseline demographic and disease characteristics (randomized population)

|                                          | Pimecrolimus cream 1%<br>(n = 100) | Vehicle cream<br>(n = 98) |
|------------------------------------------|------------------------------------|---------------------------|
| Age (years)                              |                                    |                           |
| Mean                                     | 33.1                               | 33.8                      |
| Standard deviation                       | 12.08                              | 12.70                     |
| Range                                    | 18–69                              | 18–81                     |
| Sex – n (%)                              |                                    |                           |
| Male                                     | 40 (40.0)                          | 41 (41.8)                 |
| Female                                   | 60 (60.0)                          | 57 (58.2)                 |
| Race – n (%)                             |                                    |                           |
| Caucasian                                | 93 (93.0)                          | 93 (94.9)                 |
| Black                                    | 1 (1.0)                            | 2 (2.0)                   |
| Oriental                                 | 3 (3.0)                            | 0 (0.0)                   |
| Other                                    | 3 (3.0)                            | 3 (3.1)                   |
| Baseline pruritus severity score – n (%) |                                    |                           |
| 0 (absent)                               | 1 (1.0)                            | 3 (3.1)                   |
| 1 (mild)                                 | 11 (11.0)                          | 11 (11.2)                 |
| 2 (moderate)                             | 56 (56.0)                          | 51 (52.0)                 |
| 3 (severe)                               | 31 (31.0)                          | 29 (29.6)                 |
| Missing                                  | 1 (1.0)                            | 4 (4.1)                   |
| Baseline IGA score – n (%)               |                                    |                           |
| 2 (mild disease)                         | 26 (26.0)                          | 33 (33.7)                 |
| 3 (moderate disease)                     | 74 (74.0)                          | 65 (66.3)                 |

Other secondary efficacy variables were analysed using either the ITT or pruritus ITT population. The primary efficacy variable and main secondary efficacy variable were analysed using statistical life-table methods (i.e. Kaplan–Meier estimate and log-rank test) with appropriate 'censoring' of patients who discontinued and/or completed the trial without responding. The other secondary efficacy variables were analysed using statistical life-table methods or the Z-test for proportions (with continuity correction). Safety data were mainly assessed on the frequency of AEs.

Data from all participating centres were pooled. For the main secondary efficacy variables there were two separate analyses: for 2 days' treatment and for 3 days' treatment. To account for multiple testing issues, the method of Hochberg (23) was used. This procedure was performed using a level of significance of 0.05 because the protocol prespecified that the main secondary efficacy variables would only be formally tested if the primary efficacy variable was significant at the 0.05 level of significance, i.e. the so-called 'Gatekeeper' procedure (24). No inferential statistics (conclusions extending beyond the immediate data alone) were performed for the OL extension.

## Results

### Patients

A total of 216 patients were screened and 198 patients subsequently randomized to receive pimecrolimus cream 1% (n = 100) or vehicle (n = 98). Baseline demographics were comparable in both groups (Table 1). Pruritus scores were self-reported by patients using the IVRS, however, some patients failed to report their baseline pruritus scores, and these were recorded as missing data (Table 1).

The majority of patients had moderate disease: 74% and 66% of patients in the pimecrolimus and vehicle groups, respectively, had an IGA score of 3 at baseline. The majority of patients also had moderate–severe pruritus with 87% and 82% in the pimecrolimus and vehicle groups, respectively. Although not all patients met the protocol criterion for pruritus severity, the proportions of patients with moderate to severe pruritus (via IVRS) were similar in the two analysis populations (Table 1). More than half of the patients in each treatment group had moderate pruritus at baseline, and less than one-third had severe pruritus. The proportions according to severity were consistent with those observed in the other analysis populations.

All early discontinuations because of AEs ( $n = 4$ ) occurred in the vehicle group: unsatisfactory therapeutic effect [2]; bacterial superinfection of moderate severity, not considered to be related to study medication [1] and application-site burning [1].

### Efficacy

**Core study.** Over 7 days' treatment, pimecrolimus cream 1% produced a clinically relevant, statistically significant improvement in pruritus, compared with vehicle ( $P = 0.001$ , Fig. 2). The median time to pruritus improvement ( $\geq 1$  point) was 2 days in the pimecrolimus-treated group vs 4 days in the vehicle group. Significant differences between treatment groups were observed as early as Day 2 (within 48 h of treatment): 56% of pimecrolimus-treated patients vs 34% of vehicle-treated patients reduced their pruritus scores by  $\geq 1$  point, compared with baseline ( $P = 0.003$ ).

By day 3 (within 72 h of treatment), 72% of pimecrolimus-treated patients vs 45% of vehicle-treated patients experienced  $\geq 1$ -point reduction in pruritus severity, compared with baseline ( $P < 0.001$ ).

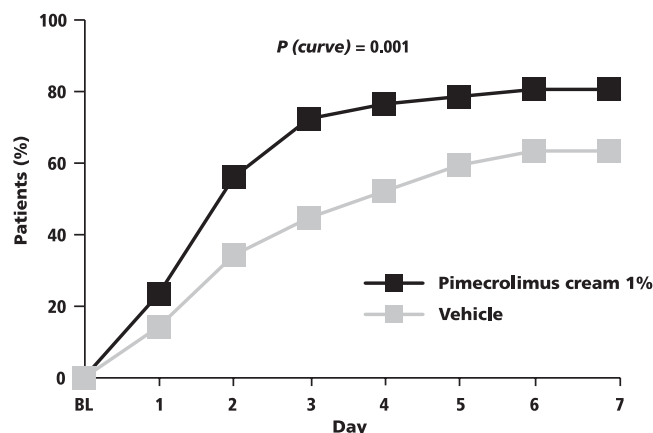


**Figure 2.** Time to first pruritus improvement of  $\geq 1$  point during the 7-day treatment period (pruritus intent-to-treat). This graph represents a cumulative response rate taken from the Kaplan–Meier estimates. Statistically significant by log-rank test, unstratified by centre-primary efficacy variable.

The significant differences in pruritus relief between treatment groups were sustained through days 4–7: 81% of pimecrolimus-treated patients vs 63% of vehicle-treated patients showed improvement ( $\geq 1$  point compared with baseline) by day 7 ( $P < 0.001$ ). Furthermore, there were significantly more patients with mild/absent pruritus in the pimecrolimus group vs the vehicle group for days 2–7 (Fig. 3). Pruritus scores of 'mild' or 'absent' were recorded by 42% of pimecrolimus-treated patients vs 27% of vehicle-treated patients ( $P = 0.04$ ) by day 2, and by 55% of pimecrolimus-treated patients vs 31% of vehicle-treated patients ( $P = 0.002$ ) by day 3. This treatment difference was maintained over 7 days: by day 7, 63% of pimecrolimus-treated patients vs 36% of vehicle-treated patients scored their pruritus severity as either 'mild' or 'absent' ( $P < 0.001$ ).

Treatment with pimecrolimus cream 1% produced greater improvements in IGA scores compared with vehicle: 53% pimecrolimus-treated patients vs 20% of vehicle-treated patients ( $P < 0.001$ ) experienced a  $\geq 1$ -point reduction in their IGA scores by day 7.

**Adverse events.** The overall incidence of AEs was similar in both treatment groups (Table 2), the majority being of mild–moderate severity. Mild–moderate nasopharyngitis was reported more frequently in the pimecrolimus group, but was not considered to be related to study medication. Overall, pimecrolimus cream 1% demonstrated a good safety profile and was well tolerated. For the 5-week, OL extension, the overall incidence of AEs was 54% (79/146 patients), including nasopharyngitis (13.7% [20/146]), headache (7.5% [11/146]), folliculitis (4.1% [6/146]), AD (3.4% [5/146]), acne (2.7% [4/146]) and pruritus (2.1% [3/146]), which were generally mild–moderate in severity. There was no increase in incidence of AEs over time.

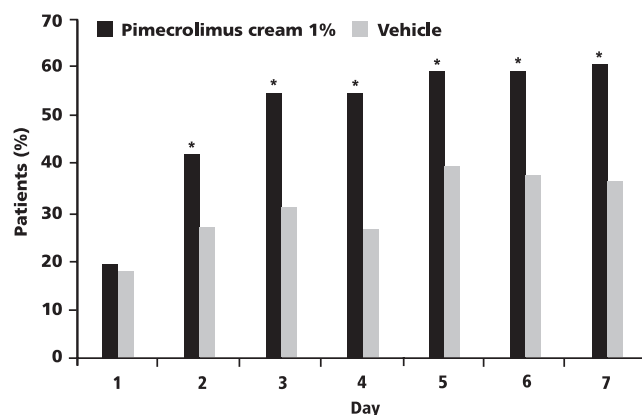


**Figure 3.** Percentage of patients with a pruritus severity score of 0 or 1 for treatment days 1–7 (intent-to-treat population). \*Statistically significant by Z-test for proportions with a continuity correction.

Table 2. Number (%) of patients with most frequent treatment-emergent adverse events ( $\geq 2\%$  for any group) (safety population)

|                                        | Pimecrolimus<br>cream 1%<br>( <i>n</i> = 100)<br>no. (%) | Vehicle<br>cream<br>( <i>n</i> = 98)<br>no. (%) | Overall<br>( <i>n</i> = 198)<br>no. (%) |
|----------------------------------------|----------------------------------------------------------|-------------------------------------------------|-----------------------------------------|
| Patients studied                       |                                                          |                                                 |                                         |
| Total number of patients               | 100                                                      | 98                                              | 198                                     |
| Total number with an adverse event     | 20 (20.0)                                                | 17 (17.3)                                       | 37 (18.7)                               |
| System organ class:                    |                                                          |                                                 |                                         |
| <i>Preferred term</i>                  |                                                          |                                                 |                                         |
| Infections and infestations            | 8 (8.0)                                                  | 6 (6.1)                                         | 14 (7.1)                                |
| Nasopharyngitis                        | 5 (5.0)                                                  | 1 (1.0)                                         | 6 (3.0)                                 |
| Folliculitis                           | 2 (2.0)                                                  | 2 (2.0)                                         | 4 (2.0)                                 |
| Skin and subcutaneous tissue disorders | 4 (4.0)                                                  | 6 (6.1)                                         | 10 (5.1)                                |
| Skin burning sensation                 | 3 (3.0)                                                  | 1 (1.0)                                         | 4 (2.0)                                 |
| Atopic dermatitis                      | 0 (0.0)                                                  | 2 (2.0)                                         | 2 (1.0)                                 |
| Eczema                                 | 0 (0.0)                                                  | 2 (2.0)                                         | 2 (1.0)                                 |
| Nervous system disorders               | 2 (2.0)                                                  | 3 (3.1)                                         | 5 (2.5)                                 |
| Headache                               | 1 (1.0)                                                  | 3 (3.1)                                         | 4 (2.0)                                 |
| Burning sensation                      | 2 (2.0)                                                  | 0 (0.0)                                         | 2 (1.0)                                 |

Adverse events are presented in descending incidence of the preferred term in the pimecrolimus cream 1%-treatment group.

### Open-label extension

Upon completion of the 7-day, randomized, DB treatment period, 146 patients entered a 5-week, OL extension study where all patients received treatment with pimecrolimus cream 1% on a patient-related need, bid basis; however, only 145 patients provided pruritus and/or IGA data during the OL extension. Pruritus and IGA scores were maintained or improved in the majority of patients. Patients who had been treated with vehicle during the core study showed greater improvement, since they 'caught up' in the OL extension with those patients treated with pimecrolimus from the beginning. Thus, of patients in the DB phase, 92% (58/63) who received vehicle and 76% (62/82) who received pimecrolimus improved or maintained their pruritus status during the 5-week extension. In total, 83% (120/145) of patients improved or maintained during the 5-week extension period, and at the end of this phase, 45% of patients scored their pruritus as 'mild' and 25% scored their pruritus as 'absent'.

The IGA scores showed similar improvement over time with 88% or more of patients improving or maintaining their status at 5 weeks.

### Discussion

Pruritus has a highly negative impact on patients' quality of life and is often one of the primary reasons for patients seeking help with their AD. Pruritus causes disruption of sleep, irritability and stress; not only for patients, but also for caregivers and other family members (25, 26). One of

the primary objectives of effective therapy is to minimize pruritus as rapidly as possible, whilst also reducing inflammation.

The results of this study demonstrated that treatment with pimecrolimus cream 1% provided noticeable improvements in pruritus in adults within 24 h, and significant relief of pruritus within 48 h (day 2), with significantly more pimecrolimus-treated patients reporting mild/absent pruritus compared with vehicle-treated patients. The differences between the treatment groups were even more significant by day 3, sustained through to study completion at Day 7. In those patients enrolled in the 5-week, OL extension, 46% showed an improvement in pruritus scores and 45% experienced improvement in IGA scores. The majority of the other patients maintained their pruritus and/or IGA scores, with the cohort previously treated with vehicle producing a higher percentage of patients who either maintained or improved their pruritus and/or IGA scores.

The speed of pruritus relief provided by pimecrolimus cream 1% is important for two reasons. First, rapid relief of pruritus is highly desirable for improving patient and caregiver quality of life (1). Secondly, rapid relief of pruritus provides the potential to control the course of AD by breaking the itch-scratch cycle. If the drug is applied at the first signs or symptoms of pruritus, physical trauma from scratching is likely to be reduced, thus minimizing or preventing the consequences of scratching, such as increased inflammation, secondary infections and progression to severe flares.

Previous studies of adults with moderate-severe AD have shown that topical calcineurin inhibitors reduce pruritus with a rapid onset of action – e.g. pimecrolimus reduced pruritus scores by day 2 (19), and tacrolimus reduced pruritus and inflammation within 3 days of initiating therapy (27).

The early effect of pimecrolimus on pruritus is particularly relevant in the long-term management of AD. As shown in three DB studies in infants, children and adults, pimecrolimus treatment prevented progression of flares when used at the first signs or symptoms of AD (pruritus, redness) (18, 19, 21).

The fast-acting nature of pimecrolimus compares favourably with published data for betamethasone dipropionate, a potent topical corticosteroid. Wahlgren et al. (28), using a visual-analogue scale, showed that betamethasone dipropionate produced a significant improvement in pruritus intensity vs vehicle by day 2 ( $P < 0.01$ ) and days 3–4 ( $P < 0.001$ ). A head-to-head study would be required to directly compare the speed of pruritus relief of betamethasone dipropionate and pimecrolimus.

A recent comprehensive review of published literature demonstrated that the evidence for antihistamine use in AD is inconclusive (7). Furthermore, although several antihistamines do relieve pruritus via central sedation, the magnitude of the effect is small (7).

In the DB phase, 76% of pimecrolimus-treated patients improved or maintained their pruritus status during the 5-week extension *vs* 92% of patients who switched from vehicle treatment in the DB phase to pimecrolimus in the extension phase. These results are consistent with those observed in previous studies where patients who switched to pimecrolimus treatment from vehicle experienced a rapid improvement in the Eczema Area and Severity Index (29, 30).

In summary, this study demonstrates that treatment with pimecrolimus cream 1% markedly reduces pruritus within 2 days in adults with mild–moderate AD and moderate–severe pruritus symptoms. When applied at first signs or symptoms, such treatment could help to break the itch–scratch cycle, thus preventing flares and controlling the course of AD. The suggested comparable speed of relief of pruritus using pimecrolimus treatment compared with betamethasone dipropionate, combined with pimecrolimus' proven safety profile and lack of systemic side-effects suggest that pimecrolimus could

provide an appealing option for the long-term treatment of AD.

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## References

- Pfeifer-Ott B, Godfrey J. Patients report many different signs and symptoms as indicators of impending flare in atopic eczema. *J Eur Acad Dermatol Venereol* 2003;**17**(Suppl. 3):181.
- McCuaig C. The itch that rashes: an update on atopic dermatitis. *Can J Diagnosis* 2003;**20**:69–76.
- Stander S, Steinhoff M. Pathophysiology of pruritus in atopic dermatitis: an overview. *Exp Dermatol* 2002;**11**:12–24.
- Giannetti A, Fantini F, Cimitan A, Pincelli C. Vasoactive intestinal polypeptide and substance P in the pathogenesis of atopic dermatitis. *Acta Derm Venereol Suppl* (Stockh) 1992;**176**:90–92.
- Stander S, Steinhoff M, Schmelz M, Weisshaar E, Metze D, Luger T. Neurophysiology of pruritus: cutaneous elicitation of itch. *Arch Dermatol* 2003;**139**:1463–1470.
- Wahlgren CF, Scheynius A, Hagermark O. Antipruritic effect of oral cyclosporin A in atopic dermatitis. *Acta Derm Venereol* 1990;**70**:323–329.
- Herman SM, Vender RB. Antihistamines in the treatment of atopic dermatitis. *J Cutan Med Surg* 2003;**7**:467–473.
- Kawashima M, Tango T, Noguchi T, Inagi M, Nakagawa H, Harada S. Addition of fexofenadine to a topical corticosteroid reduces the pruritus associated with atopic dermatitis in a 1-week randomized, multicentre, double-blind, placebo-controlled, parallel-group study. *Br J Dermatol* 2003;**148**:1212–1221.
- Boguniewicz M. Treatment options and new therapeutic approaches in atopic dermatitis. *Dermatol Nurs* 2003; (Suppl.):12–18.
- Savin JA, Paterson WD, Adam K, Oswald I. Effects of trimeprazine and trimipramine on nocturnal scratching in patients with atopic eczema. *Arch Dermatol* 1979;**115**:313–315.
- Doxepin cream for eczema? *Drug Ther Bull* 2000;**38**:31–32.
- Grassberger M, Baumruker T, Enz A, Hiestand P, Hultsch T, Kalthoff F et al. A novel anti-inflammatory drug, SDZ ASM 981, for the treatment of skin diseases: in vitro pharmacology. *Br J Dermatol* 1999;**141**:264–273.
- Kalthoff FS, Chung J, Stuetz A. Pimecrolimus inhibits up-regulation of OX40 and synthesis of inflammatory cytokines upon secondary T cell activation by allogeneic dendritic cells. *Clin Exp Immunol* 2002;**130**:85–92. Erratum in *Clin Exp Immunol* 2002;**130**:562–563.
- Winiski A, Wang S, Schwendinger B, Stuetz A. Inhibitory activity of pimecrolimus and tacrolimus on induced cytokine mRNA and protein expression in a human T-cell line (Jurkat) measured via RT-PCR and ELISA. *J Invest Dermatol* 2002;**119**:347 (Abstract 835).
- Hultsch T, Muller KD, Meingassner JG, Grassberger M, Schopf RE, Knop J. Ascomycin macrolactam derivative SDZ ASM 981 inhibits the release of granule-associated mediators and of newly synthesized cytokines in RBL 2H3 mast cells in an immunophilin-dependent manner. *Arch Dermatol Res* 1998;**290**:501–507.
- Zuberbier T, Chong SU, Grunow K, Guhl S, Welker P, Grassberger M et al. The ascomycin macrolactam pimecrolimus (Elidel, SDZ ASM 981) is a potent inhibitor of mediator release from human dermal mast cells and peripheral blood basophils. *J Allergy Clin Immunol* 2001;**108**:275–280.
- Eichenfield LF, Lucky AW, Boguniewicz M, Langley RG, Cherill R, Marshall K et al. Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. *J Am Acad Dermatol* 2002;**46**:495–504.
- Kapp A, Papp K, Bingham A, Folster-Holst R, Ortonne JP, Potter PC et al. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. *J Allergy Clin Immunol* 2002;**110**:277–284.
- Meurer M, Folster-Holst R, Wozel G, Weidinger G, Junger M, Brautigam M et al. Pimecrolimus cream in the long-term management of atopic dermatitis in adults: a six-month study. *Dermatology* 2002;**205**:271–277.

20. Queille-Roussel C, Paul C, Duteil L, Lefebvre MC, Rapatz G, Zagula M et al. The new topical ascomycin derivative SDZ ASM 981 does not induce skin atrophy when applied to normal skin for 4 weeks: a randomized, double-blind controlled study. *Br J Dermatol* 2001;**144**:507–513.
21. Wahn U, Bos JD, Goodfield M, Caputo R, Papp K, Manjra A et al. Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. *Pediatrics* 2002;**110**:e2.
22. Bernard LA, Eichenfield LF. Topical immunomodulators for atopic dermatitis. *Curr Opin Pediatr* 2002;**14**:414–418.
23. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika* 1988;**75**:800–802.
24. Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. *J Statist Planning Inference* 2001;**99**:25–40.
25. Fivenson D, Arnold RJ, Kaniecki DJ, Cohen JL, Frech F, Finlay AY. The effect of atopic dermatitis on total burden of illness and quality of life on adults and children in a large managed care organization. *J Manag Care Pharm* 2002;**8**:333–342.
26. Ben-Gashir MA. Relationship between quality of life and disease severity in atopic dermatitis/eczema syndrome during childhood. *Curr Opin Allergy Clin Immunol* 2003;**3**:369–373.
27. Kapp A, Allen BR, Reitamo S. Atopic dermatitis management with tacrolimus ointment (Protopic). *J Dermatolog Treat* 2003;**14**:5–16.
28. Wahlgren CF, Hagermark O, Bergstrom R, Hedin B. Evaluation of a new method of assessing pruritus and antipruritic drugs. *Skin Pharmacol* 1988;**1**:3–13.
29. Barbier N, Paul C, Luger T, Allen R, de Prost Y, Papp K et al. Validation of the Eczema Area and Severity Index for atopic dermatitis in a cohort of 1550 patients from the pimecrolimus cream 1% randomized controlled clinical programme. *Br J Dermatol* 2004;**150**:96–102.
30. Kaufmann R, Fölster-Holst R, Höger P, Thaçi D, Löffler H, Staab D et al. Onset of action of pimecrolimus cream 1% in the treatment of atopic eczema in infants. *J Clin Allergy Immunol* 2004;**114**:1183–1188.