

CLINICAL REPORT

An Experimental Ointment Formulation of Pimecrolimus is Effective in Psoriasis without Occlusion

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Pimecrolimus (Elidel[®], SDZ ASM 981), a new macrolactam ascomycin derivative, was highly effective in treating plaque-type psoriasis when applied under Finn-chamber occlusion. A two-centre, randomized, double-blind, vehicle- and positive-controlled within-patient study was therefore conducted in 23 adult psoriasis patients. Pimecrolimus 1% was applied, twice daily, in an experimental ointment formulation, along with the corresponding vehicle, 0.005% calcipotriol ointment and 0.05% clobetasol-17-propionate ointment to test sites without occlusion for 21 days. Erythema, induration and scaling (score: 0 [absent] to 4 [severe]) were evaluated. The total sign score was defined as the sum of the erythema, induration and scaling scores (range 0–12). Pimecrolimus 1% ointment was significantly ($p=0.03$) more effective than the corresponding vehicle, with an improvement in total sign score of 51.4% compared with 36.7% for the corresponding vehicle. Improvements with calcipotriol and clobetasol-17-propionate were 71.5% and 88.3%, respectively. No local or systemic drug-related side effects were observed in the study. We conclude that pimecrolimus 1% in the experimental ointment formulation was significantly more effective than its corresponding vehicle, but less effective than calcipotriol and clobetasol ointment. This is the first study reporting a significant therapeutic effect of pimecrolimus in an ointment formulation applied without occlusion to psoriatic plaques. *Key words:* pimecrolimus; psoriasis; topical; treatment.

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Pimecrolimus (SDZ ASM 981) is one of the new immunomodulating macrolactams. Like tacrolimus (FK506), another macrolactam compound, pimecrolimus has been shown to be effective in the topical treatment of atopic eczema in adults and in children (1–4). In psoriasis, both compounds have been found to be beneficial when used under occlusion (5, 6);

however, without occlusion tacrolimus ointment has no effect (5, 7).

Pharmacological data indicate that pimecrolimus binds to a receptor-protein in the cytosol termed FK-binding protein 12 (FKBP-12) or macrophilin 12. The pimecrolimus-macrophilin 12 complex then binds to the enzyme calcineurin phosphatase, thereby blocking its enzymatic activity. Calcineurin is a key enzyme regulating the translocation of nuclear transcription factors from the cytosol into the nucleus by dephosphorylation of their cytosolic components. The nuclear factor of activated T-cells (NF-AT) and nuclear factor kappa B (NF- κ B) are those most sensitive to the action of calcineurin. Both are key factors regulating the transcription of genes encoding cytokines such as interleukins 2, 4, 5 and 8. Interleukin 2 (IL-2) is the most important autocrine activator of T-cells. The chemokine IL-8 has been shown to attract T-cells and neutrophil granulocytes into sites of inflammation and to induce proliferation in human keratinocytes. Pimecrolimus has also been shown to inhibit mast cell activation and histamine release (8–10).

These effects of pimecrolimus are important in eczematous conditions but also in psoriasis, where T-cells and neutrophil granulocytes are the predominant cells of the inflammatory infiltrate and where abnormal keratinocyte proliferation is a hallmark of the disease (11).

METHODS

Study objective

The objective of the study was to evaluate the therapeutic effect of pimecrolimus 1% ointment and its corresponding vehicle in comparison with 0.005% calcipotriol ointment, 0.05% clobetasol-17-propionate ointment in patients with chronic plaque-type psoriasis after non-occluded application.

Study design

The study was designed as a two-centre, randomized, double-blind, vehicle- and positive-controlled, within-subject study. The study was approved by the local ethics committees of the universities of Kiel and Münster. After screening 24 patients, 23 were randomized after their written informed consent had been obtained. The mean age of the 18 male and 5 female patients was 51.1 ± 14.8 years. Inclusion criteria were:

- Clinically stable chronic plaque type psoriasis.
- Total sign score of at least 6 (sum of erythema, induration and scaling scores) – had to be comparable within a given patient (i.e. total sign score of any two test sites do not differ by more than 1 point).
- All test sites had to be either located exclusively on the trunk (including upper arm and upper leg) or located exclusively on the lower legs.
- Test sites had not to be located on the head, knee, feet, elbow, lower arm or hand.
- The test sites had to be at least 3 cm apart.
- Scaling score of 0–1 on the first treatment day. If more pronounced scaling existed, keratolytic agents (e.g. 5–10% salicylic acid in white petrolatum) were permitted during the screening phase (day –14 to –2). However, use of keratolytic treatment had to be stopped at Day –2.

Any of the following criteria disqualified a patient from participation in the study:

- Systemic therapy for psoriasis within one month prior to study treatment (PUVA, methotrexate, steroids, retinoids, cyclosporin A, herbal medicines).
- Pustular psoriasis or spontaneously flaring or improving psoriasis.
- Intake of oral medication known to precipitate psoriasis lesions.
- Topical therapy (tar, corticosteroids, dithranol, retinoids, vitamin D analogues) or phototherapy within 2 weeks prior to study treatment.

Psoriasis plaques were evaluated using a 5-point score ("total sign score") assessing scaling, erythema and induration from 0 indicating clear skin to 4 indicating a maximum expression of the respective parameter. Comparable psoriasis plaques with a sum-score of at least 6 were chosen located either on the trunk, the upper arms and the upper legs or located only on the lower legs.

At baseline the patients were randomized to receive pimecrolimus ointment 1%, its vehicle alone, calcipotriol ointment 0.005% and clobetasol-17-propionate ointment 0.05% twice daily on four comparable psoriasis plaques in a standardized way by a study nurse for 21 days. The sites were marked with ink to define round test areas of 1.5 to 2.5 cm in diameter. With a rubbing action, 2 to 3 mg/cm² of the respective formulation was applied to each test site for 15 sec. Randomization was performed for drug and localization. Evaluation of scaling, erythema and induration was performed three times per week by the same investigator.

Routine laboratory parameters such as haematology, serum liver enzymes, serum creatinine and urea were evaluated before and at the end of the treatment period. Local tolerability was assessed by both the investigator and the study nurse before the next application of the ointments.

The primary efficacy variable, i.e. the percentage change of the total sign score from baseline to the end of the study, was analysed using the Wilcoxon matched-pair signed-rank test.

RESULTS

The results of this study show that pimecrolimus ointment is significantly ($p=0.033$) superior to its corresponding vehicle control (Fig. 1). After 21 days of

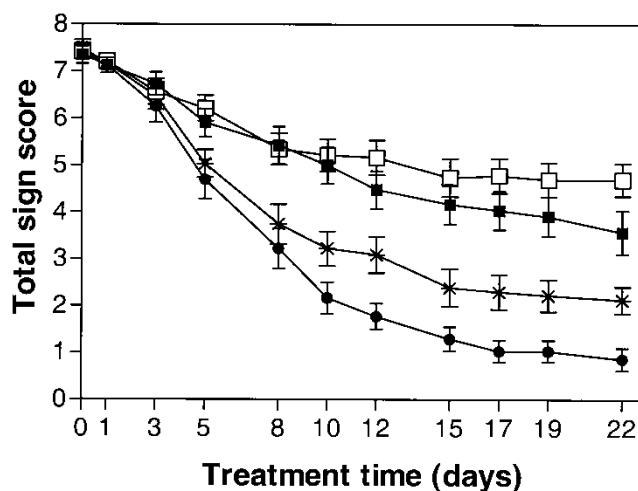


Fig. 1. Effect of pimecrolimus 1% ointment (close squares) applied twice daily without occlusion on psoriasis plaques in comparison with its vehicle (open squares), calcipotriol 0.005% ointment (stars) and clobetasol-17-propionate 0.05% (close circles) during the 21 days of treatment as assessed by the total sign-score (mean and SEM, $n=23$).

twice-daily treatment, a reduction in the baseline total sign score of 51.4% was achieved compared to its vehicle, which showed 36.7% reduction. Calcipotriol ointment demonstrated a reduction in the total sign score of 71.5% in the same time, while clobetasol-17-propionate was most effective in improving the psoriasis plaques (88.3% reduction of total sign score).

There were no local adverse events reported by the patients or by the investigators in all treatment groups. Routine laboratory examinations did not reveal any change between baseline and at the end of treatment in all groups of patients.

DISCUSSION

In this study it is shown for the first time that pimecrolimus incorporated in a new galenical formulation containing 10% urea was effective in improving psoriasis plaques by non-occluded application twice daily for 21 days. At the end of the treatment period pimecrolimus ointment was significantly more effective than its vehicle control and only slightly less effective than calcipotriol ointment. Clobetasol-17-propionate ointment was found to be the most effective medication tested in this study with non-occluded therapy of psoriasis plaques. No local or systemic side effects were observed.

In previous reports, pimecrolimus as well as tacrolimus, another macrolactam immunomodulator, were found to improve psoriasis lesions when applied topically under Finn-chamber occlusion using the psoriasis plaque assay (6). However, tacrolimus ointment failed to improve psoriasis lesions after non-occluded application (7). Interestingly, both pimecrolimus and

tacrolimus are effective in the topical treatment of atopic dermatitis (12). Therefore insufficient penetration of both compounds from the available formulations was discussed in psoriasis.

In order to increase percutaneous absorption of pimecrolimus, a new galenical formulation was introduced in which 10% urea served as a penetration enhancing compound. Using this improved ointment formulation pimecrolimus was found to be significantly superior to its vehicle, but less efficacious compared to calcipotriol ointment. Pimecrolimus was also shown not to induce skin atrophy as compared to topical corticosteroids such as betamethasone in humans (13).

The data obtained in this study provide evidence that cutaneous penetration of macrolactam compounds such as pimecrolimus can be enhanced by using adapted galenical formulations resulting in significant efficacy in the local treatment of psoriasis.

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