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ORIGINAL ARTICLE

Pimecrolimus 1% cream for the treatment of rosacea

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ABSTRACT

Rosacea is a common inflammatory skin disorder; the pathogenesis is unclear. Various treatment options for rosacea are available, but most have limited effectiveness. The aim of this study was to investigate the efficacy and safety of 1% pimecrolimus cream for the treatment of rosacea. Thirty patients with rosacea were enrolled in this 4-week, single-center, open-label study of 1% pimecrolimus cream. Patients were instructed to apply the cream to their faces twice daily and were not permitted to use any other agents. Clinical efficacy was evaluated by a rosacea grading system using photographic documentation and a mexameter. The 26 patients who completed the study experienced significantly reduced rosacea clinical scores from 9.65 ± 1.79 at baseline to 7.27 ± 2.11 at the end of treatment ($P < 0.05$). The mexameter-measured erythema index decreased significantly from 418.54 ± 89.56 at baseline to 382.23 ± 80.04 at week 4 ($P < 0.05$). The side-effects were mostly transient local irritations. The results of this study suggest that 1% pimecrolimus cream is an effective and well-tolerated treatment for patients with mild to moderate inflammatory rosacea.

Key words: **calcineurin inhibitor, pimecrolimus, rosacea.**

INTRODUCTION

Rosacea is a chronic dermatological disease characterized by recurrent episodes of flushing and erythema, complicated by papules, pustules and telangiectasia.[1] According to the National Rosacea Society Expert Committee, rosacea can be classified into four subtypes: erythematotelangiectatic, papulopustular, phymatous and ocular.[2] The pathogenesis of the disease is unclear; however, recent molecular studies suggest that an altered immune response is involved in the pathogenesis of the vascular and inflammatory disease in rosacea patients.[3] Release of inflammatory factors like eicosanoids, pro-inflammatory cytokines and nitric oxide induces angiogenesis and damages dermal constituents, which is the justification for the use anti-inflammatory or immunomodulating agents in the treatment of rosacea.[3–5]

Pimecrolimus, a calcineurin inhibitor with anti-inflammatory and immunomodulatory effects, selectively targets T cells and mast cells, preventing the production and release of cytokines and other inflammatory mediators.[6,7] Pimecrolimus has been shown to be a safe, effective therapeutic alternative to topical corticosteroids and its indications are now being extended.[7] Conflicting data regarding the effectiveness of topical pimecrolimus on rosacea have been published.[8–13] In this study, we aimed to investigate the efficacy and safety of 1% pimecrolimus cream in patients with mild to moderate rosacea.

METHODS

Patients

We conducted an open-label, uncontrolled trial of 1% pimecrolimus cream for rosacea over a 4-week period. The study was approved by the local ethics committee, and patients provided informed consent.

A total of 30 patients with a diagnosis of rosacea according to the criteria described by the Standards of the National Rosacea Society Expert Committee were enrolled in the study. Patients with mild to moderate facial rosacea were eligible for inclusion if they were at least 21 years of age and were in generally good health. Patients who had phymatous or ocular rosacea, other accompanying dermatological disorders or steroid-induced acneiform eruptions were excluded. Every patient was prohibited other treatments for rosacea including systemic and topical medications for at least 4 weeks before beginning the study.

All patients were instructed to apply 1% pimecrolimus cream twice daily for 4 weeks. During the study period, patients were asked to avoid rosacea-aggravating substances, including caffeine, spicy food, alcohol, hot fluids and fluoride. Any patient with prominent papules and pustules was examined to rule out the presence of *Demodex* folliculitis.

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Efficacy variables

Clinical evaluation and severity assessments were carried out and photographic documentation was obtained at baseline and each follow-up visit (weeks 0, 2, 4). Therapeutic response was evaluated by the rosacea clinical score, overall erythema severity, erythema index, investigator's global assessment and subjective severity index.

To evaluate the efficacy of treatment, the standard grading system for rosacea developed by the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea was used.[2,14] Primary features and global assessments were graded as absent, mild, moderate or severe (0–3), and most secondary features were graded simply as absent (0) or present (1). The rosacea clinical score represents the sum of primary features, secondary features and global assessment by both the investigator and the patient (Table 1).[13] Overall erythema severity was graded on a 4-point scale; none (0), mild (1), moderate (2), severe (3). The erythema index was measured using a mexameter (MPA5; Courage-Khazaka, Koeln, Germany). Four areas (3 cm below both pupils, nasal tip and the middle of the chin) were measured three times and the average indexes were calculated. The investigator's global assessment was evaluated using a 7-point static scoring system: (0, clear; 1, minimal; 2, mild; 3, mild to moderate; 4, moderate; 5, moderate to severe; 6, severe).[15] The subjective severity index assessment was performed using a visual analog scale (VAS) of 0–10.

Table 1. Assessment of rosacea clinical score

	0	1	2	3
Primary features				
Flushing (transient erythema)	Absent	Mild	Moderate	Severe
Non-transient erythema	Absent	Mild	Moderate	Severe
Papules and pustules	Absent	Mild	Moderate	Severe
Telangiectasia	Absent	Mild	Moderate	Severe
Secondary features				
Burning or stinging	Absent	Present		
Plaques	Absent	Present		
Dry appearance	Absent	Present		
Edema	Absent	Present		
Ocular manifestations	Absent	Present		
Peripheral locations	Absent	Present		
Phymatous changes	Absent	Present		
Global assessment				
Physician ratings by subtype	Absent	Mild	Moderate	Severe
Patient's global assessment	Absent	Mild	Moderate	Severe

Safety and tolerability

Treatment-related adverse side-effects such as burning, dryness, stinging and itching were assessed throughout the study period. All safety analyses were conducted in the intent-to-treat population.

Statistical tests

For statistical analysis, differences between parameters, except the erythema index, were assessed from the baseline to each of the visits using the Wilcoxon rank sum test. The erythema index was compared by simple repeated measures ANOVA. All analyses were performed with SPSS software ver. 15.0 and $P < 0.05$ was considered significant.

RESULTS

Patient demographics and baseline characteristics

Of the 30 patients enrolled in the study, 26 (10 men and 16 women, mean age 48.3 years) completed 4 weeks of treatment. The reasons for early dropout included non-compliance, loss to follow up and protocol non-compliance. Among the remaining 26 patients, 18 patients had erythematotelangiectatic rosacea (69.2%) and eight had papulopustular rosacea (30.8%).

Efficacy variables

Rosacea clinical score

In the 26 patients who completed treatment, the rosacea clinical score decreased significantly from 9.65 ± 1.79 at baseline (week 0) to 8.08 ± 1.65 (week 2), and 7.27 ± 2.11 at the end of study (week 4; $P < 0.05$; Table 2, Fig. 1).

The rosacea clinical score decreased from 9.28 ± 1.56 at baseline to 7.50 ± 1.79 in the erythematotelangiectatic subtype and from 10.5 ± 2.07 to 6.75 ± 2.82 in the papulopustular subtype at week 4. The difference between subtypes was not significant at any time

Table 2. Efficacy parameters over time (mean ± standard deviation)

	Week 0	Week 2	Week 4
Rosacea clinical score	9.65 ± 1.79	8.08 ± 1.65*	7.27 ± 2.11*
Overall erythema severity	1.85 ± 0.54	1.35 ± 0.56*	1.23 ± 0.86
Erythema index	418.54 ± 89.56	387.50 ± 84.96†	382.23 ± 80.04
Investigator's global assessment	3.05 ± 0.90	2.46 ± 0.81*	2.08 ± 1.20
Subjective severity index	6.12 ± 0.91	4.38 ± 0.80*	3.50 ± 1.68*

*Comparison between weeks 0 and 2 or 2 and 4, Wilcoxon rank sum test, $P < 0.05$. †Comparison between weeks 0 and 2 or 2 and 4, repeated measures ANOVA, $P < 0.05$.

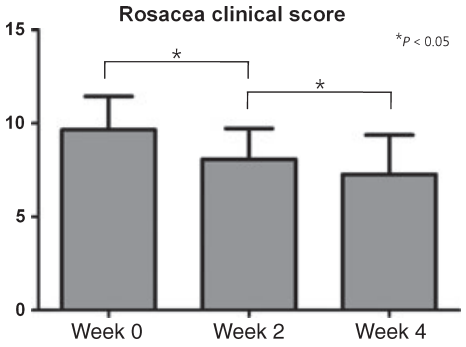

Figure 1. Rosacea clinical score at each visit.

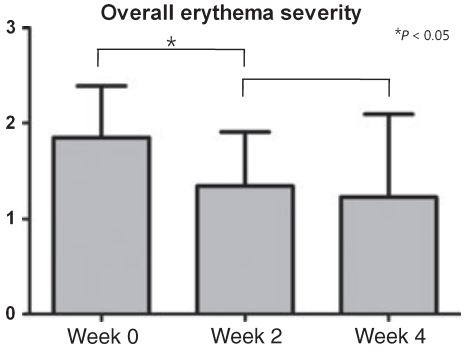

Figure 2. Overall erythema severity at each visit.

during the study ($P > 0.05$ for each visit). In addition, there was no statistical association between response to treatment and sex, age, or severity of clinical symptoms ($P > 0.05$).

Overall erythema severity

The overall erythema severity evaluated by the investigator was 1.85 ± 0.54 at baseline, 1.35 ± 0.56 at week 2 and 1.23 ± 0.86 at week 4. These scores significantly decreased during the first 2 weeks ($P < 0.05$), but did not differ significantly during the second 2 weeks ($P > 0.05$; Table 2, Fig. 2).

Erythema index

The erythema indices measured by mexameter were 418.54 ± 89.56 at baseline, 387.50 ± 84.96 at week 2 and 382.23 ± 80.04 at week 4. These measurements significantly decreased during the first 2 weeks ($P < 0.05$), but did not show a significant decline during the second 2 weeks ($P > 0.05$; Table 2, Fig. 3).

Investigator's global assessment

According to the 7-point static score, the investigator's global assessment of rosacea at baseline was 3.05 ± 0.90. This score decreased to 2.46 ± 0.81 at week 2, then 2.08 ± 1.20 at week 4. The difference between weeks 0 and 2 was statistically significant ($P < 0.05$), but the difference between week 2 and 4 was not significant ($P > 0.05$; Table 2, Fig. 4).

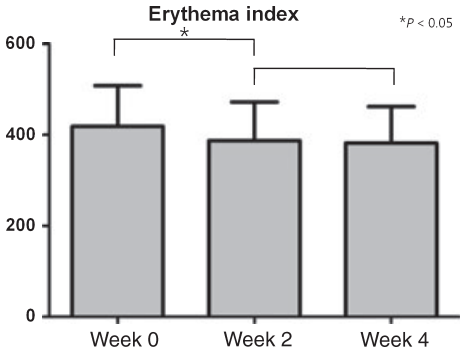

Figure 3. Erythema index at each visit.

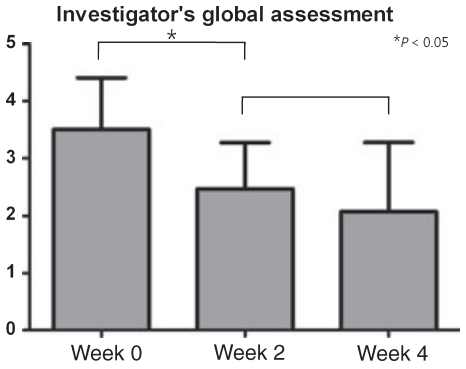

Figure 4. Investigator's global assessment at each visit.

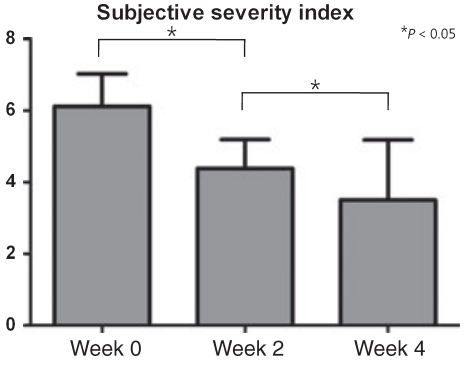

Figure 5. Subjective severity index at each visit.

Subjective severity index

As evaluated by the VAS, the subjective severity score decreased significantly from 6.12 ± 0.91 at baseline (week 0) to 4.38 ± 0.80 (week 2), and 3.50 ± 1.68 at the end of treatment (week 4; $P < 0.05$; Table 2, Fig. 5).

Relapse of symptoms

For 18 of the 26 rosacea patients who showed improvement of rosacea clinical scores, telephones surveys and physical examinations

were performed to assess long-term treatment outcomes and relapse. During the follow-up period of 21.3 months (range, 13–45 months), 15 of the 18 patients (83.3%) had relapse of symptoms after 10.4 months (range, 3–18 months) discontinuation of topical pimecrolimus. Most patients who had a relapse of rosacea reported that subjective symptoms were milder than before treatment and relatively well controlled by intermittent topical pimecrolimus.

Safety and tolerability

The most common treatment-related cutaneous adverse event was a local burning sensation reported by five of the 26 patients (19.2%). Other side-effects included itching (n = 3), dryness (n = 2) and stinging sensation (n = 1). All adverse effects were transient and mild, and did not require additional treatment.

DISCUSSION

The pathogenesis of rosacea is barely understood and the various available treatment options focus primarily on inflammation control.[5,16] They include topical medications such as metronidazole, sodium sulfacetamide, azelaic acid or tretinoin as well as systemic treatments such as tetracycline, macrolides, metronidazole or isotretinoin.[5,16] However, these treatments have not demonstrated consistent efficacy in symptom improvement and might cause resistance to antibiotics or adverse effects on hepatic and renal functions. Treatments for rosacea must address not only effectiveness but also safety, because rosacea is recurrent in nature and occurs on the face.

Topical pimecrolimus has been reported to be effective for atopic dermatitis, seborrheic dermatitis, lichen planus and cutaneous lupus erythematosus.[7,17] Although it is not generally used in rosacea, previously reported studies have shown its effectiveness in this condition. In contrast to corticosteroids, pimecrolimus does not affect endothelial cells and fibroblasts, and does not induce telangiectasia and skin atrophy.[6,7] Furthermore, because of its the inhibitory effects on pro-inflammatory mediators and cytokines, pimecrolimus is expected to be effective in patients with various forms of rosacea.[6]

Until recently, the diagnosis and classification of rosacea was ambiguous, until clinical criteria were established by the National Rosacea Society Expert Committee.[2] According to the criteria, rosacea is classified into four clinical subtypes, namely, erythematotelangiectatic, papulopustular, phymatous and ocular. Steroid-induced rosacea is not included and is categorized as a separate disease: steroid-induced rosacea-like eruptions.[2,14] Patients with steroid-induced rosacea were excluded from this study; only patients with erythematotelangiectatic type and papulopustular type were enrolled. Although these two types seem to share some clinical feature similarities, there are distinct differences in treatment response.

In previous studies, steroid-induced rosaceaiform eruptions were successfully managed with pimecrolimus cream.[14,18,19] Lee *et al.*[18] reported the effective treatment of 18 patients with steroid-induced rosacea using pimecrolimus cream. However, the effects of pimecrolimus cream on rosacea remain subject to debate. The results of early open-label studies were relatively good,[8,9] but no effects have been reported in recent studies.[10,12] In 2005, Crawford *et al.*[8] investigated the efficacy of pimecrolimus cream in 12 patients with erythematotelangiectatic or papulopustular rosacea and reported substantial improvement of erythema in 10 patients and a decreased papulopustular component in five patients. Cunha *et al.*[9] reported dramatic clearing of a granulomatous rosacea with 4.5 months of pimecrolimus therapy. However, Weissenbacher *et al.*[10] reported that treatment for 4–8 weeks with pimecrolimus cream was not more efficacious than the vehicle cream (n = 40). In 2009, Koca *et al.*[13] in comparative studies of pimecrolimus and metronidazole cream, reported that both treatments were very effective in papulopustular rosacea, but there were no significant differences between the two treatments. These conflicting results prompted us to conduct trials to determine the effectiveness of pimecrolimus cream against rosacea.

This study yielded the following results. First, of the total 26 patients, approximately two-thirds experienced improvements in their clinical symptoms (Figs 6,7). Second, we observed

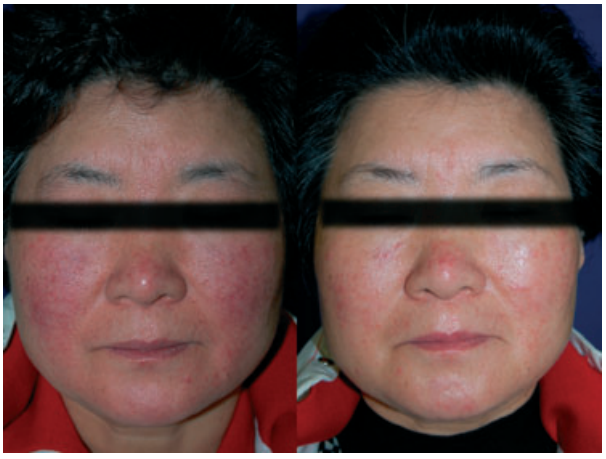

Figure 6. Improvement in a patient with erythematotelangiectatic rosacea after 4 weeks of pimecrolimus therapy.

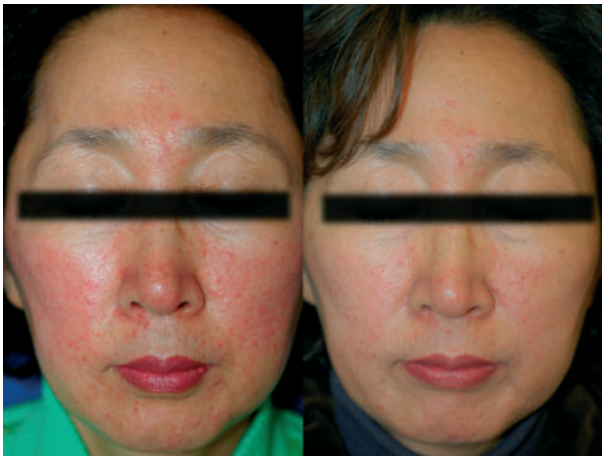

Figure 7. Improvement in a patient with papulopustular rosacea after 4 weeks of pimecrolimus therapy.

significant reduction in five efficacy variables (rosacea clinical score, overall erythema severity, erythema index, investigator's global assessment and subjective severity index). Third, the greatest response was observed in the first 2 weeks of therapy, while symptom improvement plateaued in the following 2 weeks. We think the rapidity of improvement in the initial 2 weeks represents a significant therapeutic effect. Fourth, the erythema index as measured by mexameter also improved significantly with treatment. This result is consistent with previous studies that have demonstrated a positive response to pimecrolimus cream in the treatment of rosacea. No statistical differences were observed when treatment responses were segregated by sex, age or severity of clinical symptoms as measured by the rosacea clinical score. Patients with papulopustular rosacea showed a greater reduction in rosacea clinical score than those with erythematotelangiectatic rosacea, but the difference was not statistically significant. This is different from previous results which suggest that erythematotelangiectatic rosacea might respond better to pimecrolimus than papulopustular rosacea. Finally, long-term follow-up results with topical pimecrolimus were disappointing. Although clinical improvement was observed during treatment, cutaneous lesions deteriorated after withdrawal of topical pimecrolimus. However, subjective symptoms in relapsed patients were milder than before treatment and intermittent topical pimecrolimus was well-tolerated and effective. This results supports that continuous and long-term treatment is needed to control rosacea.

The most common adverse effects of pimecrolimus cream were burning and irritation.[7,17] Our patients also reported local burning sensation (19.2%), but those were mild and transient. Overall, topical pimecrolimus cream was well-tolerated and compliance was good. In some patients with rosacea, sudden aggravation occurs after applying topical agents.[20,21] This might be the result of local immunosuppression induced by the occlusive properties of topical medications and the proliferation of *Demodex folliculorum*. In order to prevent this sudden onset of rosaceaiform dermatitis, we performed extractions in all cases of papulopustular rosacea to exclude demodicidosis. We thus avoided sudden worsening of symptoms in our patients.

Because this study is not randomized, double-blinded or vehicle-controlled, it is difficult to demonstrate effects in comparison with a control group. Despite this limitation, however, rosacea clinical score and overall erythema severity showed significant improvement even after 2 weeks of treatment. Furthermore, unlike other studies, we measured the degree of erythema using a mexameter to enhance objectivity. We also used the more detailed grading system utilized by the National Rosacea Society Expert Committee to evaluate rosacea clinical scores.[14]

Our results suggest that 1% topical pimecrolimus cream is a safe and effective therapeutic option for the treatment of rosacea. Pimecrolimus cream has also shown excellent results in patient satisfaction and rapid therapeutic effects. In conclusion, pimecrolimus cream is a promising alternative treatment for mild to moderate rosacea.

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