A comparison of metronidazole 1% cream and pimecrolimus 1% cream in the treatment of patients with papulopustular rosacea: a randomized open-label clinical trial

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Summary

Background. There are various treatment options available for rosacea, depending on the subtype, but treatment is still generally unsatisfactory. Some reports have indicated beneficial effects of topical pimecrolimus.

Aim. To compare the efficacy and safety of pimecrolimus 1% cream and metronidazole 1% cream in the treatment of patients with papulopustular rosacea (PR).

Methods. A group of 49 patients with PR was investigated in this single-centre, randomized, open-label study. Patients were randomly assigned treatment with either pimecrolimus 1% cream or metronidazole 1% cream for 12 weeks. Response was evaluated by the inflammatory lesion count, the severity of facial erythema and telangiectasia, Physician’s Global Assessment (PGA), and safety and tolerability at baseline and at weeks 3, 6, 9 and 12.

Results. In total, 48 patients completed the study. Both treatments were very effective in the treatment of PR. There were no significant differences between the treatments in inflammatory lesion counts, overall erythema severity scores and PGA evaluated from baseline to week 12 \((P > 0.05)\). Neither treatment produced any clinically relevant improvement in telangiectasia.

Conclusion. Pimecrolimus cream is no more efficacious than metronidazole cream in the treatment of PR.

Introduction

Rosacea is a chronic dermatological disease characterized by recurrent episodes of flushing and facial redness, complicated by papules, pustules, telangiectasia, oedema and tissue fibrosis in a symmetrical facial distribution. The signs of rosacea are usually confined to the face, but may appear on the neck, scalp, trunk or limbs. Initially, the hyperaemia may be episodic, but after several months to years, it becomes chronic with the development of telangiectasias. During the inflammatory episodes, papules, pustules and swelling occur. The prevalence of rosacea is highest among fair-skinned people and it occurs most commonly among adults aged 30–60 years.

According to the National Rosacea Society Expert Committee, rosacea can be classified into four subtypes: erythematotelangiectatic, papulopustular, phymatous and ocular. The cause of rosacea remains unknown. Several factors have been implicated in its pathogenesis. Proposed aetiologic mechanisms can be grouped into the following categories: vasculature, climatic exposure, matrix degeneration, chemicals and ingested agents, pilosebaceous unit abnormalities, and microbial organisms. It is known is that inflammation plays an important role in lesion formation. Release of pro-inflammatory cytokines and degradative enzymes induces angiogenesis and damages dermal constituents.
Although the aethiopathogenesis of rosacea is poorly understood, there are various treatment options available depending on the subtypes, but treatment of rosacea is still unsatisfactory. The current treatments for rosacea include topical medications such as metronidazole, azelaic acid or tretinoin, or systemic medications such as tetracyclines, azithromycin, metronidazole or isotretinoin. Avoidance of sun and of other trigger factors is also important in management of rosacea.

Topical metronidazole preparations at various concentrations (0.5–1.0%) and formulations (cream or gel) are most commonly used as monotherapy or in combination with oral antibiotics. This drug has been shown to be effective for the treatment of moderate to severe rosacea.

Pimecrolimus, an ascomycin derivative, is a topical calcineurin antagonist that inhibits T-cell and mast-cell activation by blocking the action of calcineurin, preventing the production and release of cytokines and other inflammatory mediators. Several articles have reported that pimecrolimus is effective in various forms of rosacea. Although pimecrolimus appears to be an effective option for the treatment of rosacea, we could find no study in the literature comparing it with other effective therapies. Thus, the aim of our study was to compare the efficacy and safety of topical pimecrolimus 1% cream with that of topical metronidazole 1% cream in the treatment of patients with papulopustular rosacea (PR).

**Methods**

**Study**

The study was approved by the ethics committee of the university hospital of Zonguldak Karaelmas University medical faculty, and each participant gave signed written consent after being informed about the purpose and the procedure of the study. The study was designed as a single-centre, randomized, open-label comparison of metronidazole 1% cream (Roza; Orva Pharmaceutical Industry, Istanbul, Turkey) and pimecrolimus 1% cream (Eldel; Novartis Pharma GmbH Wehr, Germany) in patients with PR. A double-blind format was not used, because the study drugs were commercial products that were not label-blinded, and the sizes and shapes of the tubes were different. Patients were randomly assigned to receive either pimecrolimus 1% cream or metronidazole 1% cream twice daily for 12 weeks. Measurements were taken at baseline and at the end of weeks 3, 6, 9 and 12.

### Table 1 Patient demographics and baseline characteristics.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Metronidazole (n = 24)</th>
<th>Pimecrolimus (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>50.7 ± 9.1</td>
<td>48.4 ± 9.4</td>
</tr>
<tr>
<td>Gender (M/F), n (%)</td>
<td>16 (66.7)/8 (33.5)</td>
<td>13 (52)/12 (48)</td>
</tr>
<tr>
<td>Mean disease duration, months*</td>
<td>16.8 ± 18.3</td>
<td>33.7 ± 33.4</td>
</tr>
<tr>
<td>Mean inflammatory lesion count, n</td>
<td>16.0 ± 4.6</td>
<td>26.0 ± 11.7</td>
</tr>
<tr>
<td>Mean erythema score</td>
<td>1.7 ± 0.4</td>
<td>2.0 ± 0.6</td>
</tr>
<tr>
<td>Mean telangiectasia score</td>
<td>1.7 ± 0.6</td>
<td>1.5 ± 0.5</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD (%) unless otherwise indicated. *P < 0.05.

**Patients**

Patients were recruited from the Department of Dermatology at Zonguldak Karaelmas University. In total, 49 patients with a diagnosis of PR according to the criteria given by the Standards of the National Rosacea Society Expert Committee, with at least 10 inflammatory lesions (papules/pustules) and who were at least 18 years of age, were included in the study. All of the patients were white. The baseline characteristics in terms of demographic data (except the disease duration) and disease activity (inflammatory lesions and severity of erythema and telangiectasia) of both groups were found to be comparable, as summarized in Table 1. The disease duration was longer in the pimecrolimus group than in the metronidazole group.

Some patients had used a treatment previously for their rosacea (4 of 25 patients in pimecrolimus group and 13 of 24 patients in metronidazole group). Patients were required to complete a washout period of 2 weeks for topical therapy with antibiotics, retinoids, corticosteroids, or nonsteroidal ant-inflammatory drugs (NSAIDs), 4 weeks for systemic therapy with antibiotics, corticosteroids or NSAIDs, and at least 6 months for oral isotretinoin. Patients who had erythematotelangiectatic, phymatous or ocular rosacea, concomitant dermatological disorders, steroid-induced rosacea or an allergy to any component of the study medications, or who were taking medications (vasodilators, β-adrenergic receptor-blocking agents or anticoagulants) that may interfere the course of rosacea, or who were pregnant or nursing were excluded from the study.

Patients were randomly assigned to receive topical metronidazole 1% cream (n = 24) or topical pimecrolimus 1% cream (n = 25) and instructed to apply the medication in a thin film to the entire face twice daily, in the morning and evening, for 12 weeks. Randomization
was carried out using random-number generation from standard tables. All patients were also given sunscreen with a sun protection factor of 20 (the same commercial preparation for both groups). Patients were also instructed to avoid rosacea-aggravating substances including caffeine, alcohol, hot beverages and spicy foods, and to avoid use of any other systemic or topical preparation.

Assessments

The same investigator carried out all evaluations at each visit. At baseline, general patient data including demographics and rosacea history were recorded. The efficacy of the treatment was assessed by counting the number of inflammatory lesions (papules/pustules) and by rating the severity of erythema and telangiectasia. The primary efficacy endpoints were the change in inflammatory lesion count and in severity of erythema and telangiectasia from baseline to last visit. Secondary efficacy parameters included change in inflammatory lesion count and in severity rating for erythema and telangiectasia from baseline to each of weeks 3, 6 and 9. Physician’s Global Assessment (PGA) of rosacea was made at the endpoint by means of a 6-point scale [1 = complete improvement (100% clearance of disease signs), 2 = marked improvement (75–99% clearance), 3 = moderate improvement (50–74% clearance), 4 = insufficient improvement (< 50% clearance), 5 = no detectable improvement from baseline] and 6 = deterioration].

Overall facial erythema and telangiectasia was graded on a four-point scale \( v \) [0 = none; 1 = mild (slight, either with restricted central involvement or generalized over the whole face); 2 = moderate (pronounced, centrally restricted or generalized on the face); 3 = severe (severe over the whole face), as was telangiectasia \( v \) [0 = none, 1 = mild (fine vessels < 0.2 mm in diameter covering < 10% of the face); 2 = moderate (several fine vessels and/or a few large vessels > 0.2 mm in diameter covering 10–30% of the face); 3 = severe (many fine and/or large vessels covering < 30% of the face)].

Safety and tolerability

Treatment-related adverse events (AEs) (dryness, increased erythema, pruritus, stinging and burning) were recorded throughout the study period at each visit on a four-point scale (0 = absent, 1 = mild, 2 = moderate or 3 = severe). All safety analyses were conducted in the intent-to-treat population.

Statistical analysis

Differences in age and disease duration of both groups were evaluated by Student’s t-test. The Kolmogorov–Smirnov test was used for normality test of variables. Treatment differences of mean inflammatory lesion count in each visit were evaluated with ANCOVA, using the number of lesions at baseline and the disease duration as covariate variables thus eliminating the effect of both variables in both treatment groups. In addition, simple repeated measures ANOVA was used to analyse differences between baseline and visits in each treatment group. The \( \chi^2 \) test was used to compare differences in erythema and telangiectasia scores from baseline to each visit, differences in PGA from baseline to the study endpoint, and frequency of AEs. Differences in erythema and telangiectasia scores from baseline to each of the study visits were assessed using the Wilcoxon signed rank test with Bonferroni adjustment.

Statistical analyses were performed on all patients randomized into the study (intent-to-treat). SPSS software (version 11.5; SPSS Inc., Chicago, IL, USA) was used for all analyses, and \( P < 0.05 \) was considered significant.

Results

Of the 49 patients enrolled into the study, 48 (24 in each group) completed 12 weeks of treatment; one patient in the pimecrolimus group discontinued the study because of deterioration of the disease.

Assessment of efficacy

Inflammatory lesions. Both treatment groups had a significant decrease in number of inflammatory lesions during the treatment period \( (P < 0.01) \), but the difference between treatments was not significant at the end of the 12th week \( (P = 0.55) \). The mean number of inflammatory lesions decreased from 16.0 ± 4.6 at baseline to 0.6 ± 1.5 at week 12 and from 26.0 ± 14.4 to 3.7 ± 6.8 in the metronidazole and pimecrolimus groups, respectively (Fig. 1a, Table 2). There was no significant difference between treatments in mean inflammatory lesion counts at any evaluation time during the study \( (P > 0.05) \) for each visit.

Erythema and telangiectasia. Both treatments achieved a significant decrease in erythema score over time \( (P < 0.05) \), but the treatments did not differ significantly in the change in severity scores from baseline to week 12 \( (P = 0.23) \). The mean erythema
score decreased from 1.75 ± 0.44 at baseline to 0.83 ± 0.56 at week 12 and from 2.00 ± 0.58 to 1.08 ± 0.49 with metronidazole and pimecrolimus, respectively (Fig. 1b). At the sixth week of the study, the reduction in erythema severity score (ESS) was better with metronidazole than with pimecrolimus (P = 0.027), and by the last visit of the study, the mean reduction in ESS was of 45.8% with metronidazole and 44.7% with pimecrolimus. Overall ESS did not differ significantly between the treatment groups at weeks 3 and 9 (P > 0.05). There was no clinically significant improvement in telangiectasia severity score (TSS) in either treatment group, and the difference in TSS between the two groups was not significant (P > 0.05).

Physician’s Global Assessment. Physician’s Global Assessment of rosacea was assessed at the study endpoint. Complete clearance was achieved by 83.3% in metronidazole group and 48.0% in the pimecrolimus group, while marked improvement was seen in 16.7% of patients in the metronidazole group and 40.0% in pimecrolimus group (Fig. 1c). Although there were more patients with complete improvement in the metronidazole group, there was no significant difference in PGA between treatments at the end of the study (P > 0.05).

Safety and tolerability. The topical preparations of both drugs were well tolerated by both treatment groups. No serious or systemic AEs were reported in either group. The most common treatment-related cutaneous AEs were a burning and stinging sensation in metronidazole group (four patients) and itching in pimecrolimus group (two). These AEs were of mild severity and transient in nature in the pimecrolimus group, but they continued with each application in the metronidazole group. However, the patients reported that both treatments were tolerable, and none of the patients discontinued the study because of AEs.

Discussion

This randomized study compared the efficacy and safety of pimecrolimus 1% cream with a widely used topical therapy (metronidazole 1% cream) in patients with PR. Both topical preparations led to a clinically relevant improvement in inflammatory lesions. We found that after 12 weeks of treatment, pimecrolimus cream was no more efficacious than metronidazole cream in treating rosacea. Both treatments are equally effective in reducing the number of inflammatory lesions and the
ESS. Both treatment groups experienced a continuous decline in mean inflammatory lesion counts throughout the 12 weeks.

The safety of topical metronidazole has been established through many years of worldwide clinical use. It has been shown to be safe and effective in PR. The erythema-reducing effect of topical metronidazole is limited. Although the mechanism of action of metronidazole is not completely understood, an anti-inflammatory effect that interferes with neutrophil release of reactive oxygen species may be the basis of its mechanism in the treatment of rosacea.\textsuperscript{18}

Pimecrolimus inhibits the activation of T cells and mast cells after antigen-specific or nonspecific stimulation. It blocks the action of calcineurin, resulting in downregulation of production of T-helper (Th1) (interleukin-2, interferon-\(\gamma\)) and Th2 (interleukins 4 and 10) cytokines.\textsuperscript{10} Topical pimecrolimus has been shown to be safe and effective for the treatment of atopic dermatitis (AD) in children and adults.\textsuperscript{19} Although it is not used routinely to treat rosacea, studies have shown its effectiveness in patients with various forms of rosacea.\textsuperscript{11–15} Crawford \textit{et al.} studied the efficacy of topical pimecrolimus for rosacea and found that pimecrolimus was effective in the treatment of erythematolangiectatic rosacea and PR. They reported that pimecrolimus could be considered in patients with recalcitrant disease.\textsuperscript{13} A study by Weissenbacher \textit{et al.} found that topical pimecrolimus was no more efficacious than treatment with the vehicle cream;\textsuperscript{11} however, there were several limitations to that study, including short treatment duration (4–8 weeks), the particular vehicle cream used as the control preparation and the type of rosacea (patients with steroid-induced rosacea were also included). The mechanism of action of pimecrolimus in rosacea is not clear. Its effect on the immune system and inflammatory processes may have an important role. It also blocks the release of histamine by mast cells,\textsuperscript{10} which may explain its efficacy in reducing the flushing attacks and improving the oedema in rosacea.

Rosaceiform dermatitis has been reported during treatment with pimecrolimus.\textsuperscript{20–23} Pimecrolimus was used in patients with a diagnosis of AD or seborrhoeic dermatitis, but a rosacea-like eruption developed during the treatment. Skin surface biopsies revealed increased numbers of \textit{Demodex} mites in follicles. The possible mechanism of this eruption was related to the local immunosuppressive effect of pimecrolimus, which may facilitate overgrowth of follicular \textit{Demodex} in susceptible patients. Although further studies are needed to clarify the causal relationship between pimecrolimus and rosaceiform reaction, clinical signs of \textit{Demodex} infection (flare of papules and pustules) should be monitored during long-term treatment with topical pimecrolimus cream.

In our study, no serious or systemic AEs were reported in either treatment group. Topical pimecrolimus is produced in a cream base and has good local tolerability. Only two patients using pimecrolimus had an itching sensation. These events were mild and transient in nature, and as the treatment was proving effective, the patients continued to use it. It has been reported that treatment compliance in patients using pimecrolimus cream for various forms of rosacea was good. The most reported side-effect was a transient burning sensation.\textsuperscript{13,15} In our study, although the efficacy of pimecrolimus cream was not superior to metronidazole cream, patients who used pimecrolimus stated that pimecrolimus was acceptable to use due to its minimal side-effects and cosmetic appeal.

In conclusion, pimecrolimus cream is no more efficacious than metronidazole cream in the treatment of patients with PR. Safe and nonirritant treatment in chronic inflammatory diseases, particularly those on the face, is an important goal. Rosacea is characterized by remissions and exacerbations. Owing to the chronic nature of the disease, there is a necessity for safe and effective long-lasting topical treatments. Because of its efficacy and minimal side-effects, pimecrolimus cream is a promising alternative treatment for recalcitrant rosacea. However, it is an expensive medication compared with metronidazole.

There were several limitations to our study: it was not double-blind, it lasted only 12 weeks and it had a small number of patients. Multicentre, double-blind studies with a longer treatment are needed to confirm the effectiveness of pimecrolimus in the management of rosacea.

\textbf{References}

Comparison of metronidazole and pimecrolimus in papulopustular rosacea • R. Koca et al.
