Treatment of Oral Erosive Lichen Planus With 1% Pimecrolimus Cream

A Double-blind, Randomized, Prospective Trial With Measurement of Pimecrolimus Levels in the Blood

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Objectives: To evaluate the efficacy of 1% pimecrolimus cream in treating oral erosive lichen planus and to assess its tolerance.

Design: Double-blind randomized trial with placebo control.

Setting: Outpatients of the Department of Dermatology, University Hospital of Nice, from December 21, 2004, to April 19, 2005.

Patients: Fourteen consecutive patients with oral erosive lichen planus confirmed by histological examination and with a clinical score superior to 3. Of the 14 patients, 2 did not meet the inclusion criteria and 12 were enrolled in the trial.

Intervention: The intervention was 1% pimecrolimus cream or its vehicle, which was applied on ulcerated lesions twice a day for 4 weeks.

Main Outcome Measures: The efficacy of the treatment was quantified using a 12-point clinical score. The blood level of pimecrolimus was analyzed on days 0 (baseline), 14, and 28.

Results: In the placebo group, the mean score was 4.67 on day 0 vs 3.33 on day 28 (P=.22). In the pimecrolimus group, the mean score was 6.83 on day 0 vs 3.33 on day 28 (P=.04). In the pimecrolimus group, blood concentrations of pimecrolimus were always above the threshold (mean value, 2.84 ng/mL; extreme values, 0.6-1.9 ng/mL). Pimecrolimus cream was well tolerated, and only transient burning sensations were reported by some subjects. Each of the patients in the pimecrolimus group whose condition improved subsequently relapsed when assessed 1 month after treatment.

Conclusions: The 1% pimecrolimus cream seems to be an effective and well-tolerated treatment for oral erosive lichen planus. The finding of systemic levels of pimecrolimus after mucosal applications necessitates long-term study because it seems that long-term application is required to maintain clinical improvement.

Trial Registration: clinicaltrials.gov Identifier: NCT00321750

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Oral erosive lichen planus (OELP) is a severe form of mucosal lichen planus. Lesions are often intensely painful, and pain when eating can lead to weight loss. A long-term course is punctuated by intermittent flares. Spontaneous remissions are rare. Treatment is difficult: topical corticosteroids are usually prescribed first, but antimalarial agents, oral retinoids, systemic corticosteroids, immunosuppressive drugs, and even extracorporeal photochemotherapy can be necessary in severe cases. There is a need for novel therapies that are effective and produce less morbidity. The anti-inflammatory action of calcineurin inhibitors provides a rational basis for using these topical agents in patients with OELP, and several open-label studies using topical tacrolimus demonstrated effectiveness. The effectiveness of 1% pimecrolimus cream in OELP has also been suggested in a few case reports and in 1 recent comparative study. The absorption of pimecrolimus through human mucosa has not been adequately studied. Its application on the ulcerative lesions of OELP could produce significant systemic levels of the drug.

See also pages 463, 511, and 519

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The objectives of this study were to evaluate the efficacy of 1% pimecrolimus cream in treating OELP, to assess its tolerability, and to evaluate the potential for systemic adverse
effects by monitoring the blood levels of this drug during the treatment period.

**METHODS**

**STUDY DESIGN**

Fourteen consecutive outpatients seeking treatment for OELP in the Department of Dermatology, University Hospital of Nice, were assessed for eligibility for this study from December 21, 2004, to April 19, 2005. Of the 14 patients, 2 did not meet the inclusion criteria and 12 were enrolled in a randomized, double-blind, controlled trial. Randomization into 2 groups was done by draw lots, with equilibration every 4 subjects. The study was approved by the ethics committee of Nice.

**PATIENTS**

The inclusion criteria included confirmation of the diagnosis of OELP by histological examination of an oral biopsy specimen and a clinical score higher than 3. Clinical history and careful histological examination, including the type and the localization of the inflammatory infiltrate and the presence of cytoid bodies, were done to differentiate OELP from lichenoid reactions. Exclusion criteria were patients younger than 18 years, pregnancy or breastfeeding, malignancy, severe or recurrent infections, uncontrolled chronic disorders, congenital or acquired immunosuppression, and concomitant treatments potentially effective on OELP, such as antimalarial agents, oral retinoids, corticosteroids, or immunosuppressive drugs.

**INTERVENTION**

The intervention was 1% pimecrolimus cream or its vehicle, which was applied on ulcerated lesions twice a day for 4 weeks. Pimecrolimus cream and placebo cream were provided by Novartis Pharma AG, Basel, Switzerland. The placebo cream was the excipient of pimecrolimus. Pharmacological studies have already been performed by Novartis Pharma AG (unpublished data, 2004), and have shown no toxicity when this cream is applied on mucosa. No eating, drinking, or gum chewing was permitted for 30 minutes after the ointment was applied.

**EVALUATION**

Clinical evaluation was performed by a single physician (T.P.). The efficacy of the treatment was quantified using a calculated score. The scoring system was described in a previous study. Briefly, spontaneous and meal-triggered pain were scored from 0 to 4 using a visual analog scale. The surface area of the erosions was evaluated using a drawing in which the areas of various zones of the mouth were indicated as a percentage of the whole surface area of the oral mucosa. Involvement of less than 5% was scored as 1; 5% to 15%, 2; 16% to 25%, 3; and more than 25%, 4. The sum of the 3 items gave a maximal possible score of 12. Clinical evaluation (including blood pressure) was performed weekly, and photographs were obtained every week as well. All adverse events were documented. Blood cell count, a complete metabolic panel (including red blood cell count, white blood cell count, platelet count, hemoglobin level, hypernatremia, hyperkalemia, hyperchloremia, and levels of serum urea nitrogen, creatinine, glucose, total bilirubin, total cholesterol, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, and pancreatic enzymes), and blood level of pimecrolimus were determined on day 0 (D0) (baseline), day 14 (D14), and day 28 (D28). The determination of blood level of pimecrolimus was performed by Novartis Pharma AG with the high-performance liquid chromatography–mass spectrometry method using 250 µL of blood (quantification threshold, 0.3 ng/mL). Use of cream was evaluated by weighing used tubes at the end of the study. A subjective assessment of the efficacy of the treatment was also asked of the patients at the end of the study (score: worse, no effect, or mild, moderate, or important improvement).

**STATISTICAL ANALYSIS**

The evolution of score within each group between D0 and D28 was analyzed by using the Wilcoxon signed rank test. The comparison of the quantity of cream used between the 2 groups was analyzed by using the nonparametric signed Mann-Whitney test.

Six patients received the pimecrolimus cream, and 6 others received placebo (Table). All the patients had already received at least 1 other treatment. The mean duration of OELP was 12 years (range, 2-58 years) (placebo group, 7 years; and pimecrolimus group, 16 years). One patient (patient 9 in the placebo group) discontinued the study on D14 because his condition failed to improve. Results were analyzed in the intent-to-treat population. There was no statistically significant difference in score between the 2 groups at the onset of the study (4.67 for the placebo group vs 6.83 for the pimecrolimus group; \( P = .39 \)). In the placebo group, the total score improved in 3 patients (only 1 had a decrease in score of \( >3 \) points). The mean score was 4.67 on D0 vs 3.33 on D28 (\( P = .22 \)). In the pimecrolimus group, the total score improved in 5 patients (all had a decrease in score of \( >3 \) points). The mean score was 6.83 on D0 vs 3.33 on D28 (\( P = .04 \) (Figure 1). The mean score of erosions was 1.67 on D0 vs 1.33 on D28 in the placebo group and 2.17 on D0 vs 0.83 on D28 in the pimecrolimus group (Figure 2).

In the pimecrolimus group, all the patients but 1 reported a moderate to important improvement of their symptoms and were satisfied by the treatment. This improvement was observed from the first week of treatment, usually within the first 2 days, and most notably patients reported less pain when eating. The clinical improvement of 1 patient is demonstrated in Figure 3. In the placebo group, only 1 patient reported moderate improvement and a modest decrease in pain when eating.

The treatment was well tolerated in both groups, but burning sensations in the first days of treatment were reported by 2 patients in the pimecrolimus group. The blood pressure remained stable in all the patients. Laboratory analyses demonstrated no abnormalities. Pimecrolimus was never detected in the blood of the control group. In the pimecrolimus group, most of the blood concentrations of pimecrolimus were higher than the threshold. The mean value was 2.32 ng/mL (extremes, 0.6-10 ng/mL) at D14 and 2.84 ng/mL (extremes, 0.6-19 ng/mL) at D28.

The mean quantity of cream used during the month of treatment was not statistically different between the pimecrolimus and placebo groups (34 vs 50 g; \( P = .42 \)). All the patients in the pimecrolimus group whose condition improved had a relapse within the month following the end of the treatment.
The significant decrease in severity score observed in the pimecrolimus group demonstrates the effectiveness of 1% pimecrolimus cream in treating OELP. Because of the few patients in this study, caution must be exercised when considering the clinical significance of this treatment. However, the objective measures are supported by the subjective reports of improvement in erosions and pain when eating, beginning early in the treatment course. More important, all the patients in the pimecrolimus group but 1 have reported a moderate to important improvement of their disease and were satisfied by the treatment. However, the treatment did not produce long-lasting benefits. All of the patients with OELP whose condition improved during the treatment period relapsed within 1 month after treatment was discontinued. These results corroborate previous observations and studies performed with topical pimecrolimus.

Pimecrolimus cream was well tolerated, with transient burning sensations noted during the first 2 weeks of therapy.}

Table. Population and Results

<table>
<thead>
<tr>
<th>Patient No./Sex/Age/ Treatment</th>
<th>Onset of Disease, y</th>
<th>Previous Treatment (Effectiveness)</th>
<th>Score at D0</th>
<th>Score at D28</th>
<th>Blood Level of ( H_{2}O_{2} ) mg/mL‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/73 1% Pimecrolimus cream</td>
<td>25</td>
<td>Betamethasone valerate cream (-)</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>2/M/79 1% Pimecrolimus cream</td>
<td>58</td>
<td>Betamethasone cream (+) and tacrolimus mouthwash (-)</td>
<td>4</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>3/F/66 Placebo</td>
<td>3</td>
<td>Betamethasone cream (+) and antimalarial agent (-)</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4/M/70 Placebo</td>
<td>5</td>
<td>Betamethasone cream (+) and antimalarial agent (+)</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5/F/77 1% Pimecrolimus cream</td>
<td>5</td>
<td>Betamethasone cream (+) and tacrolimus mouthwash (-)</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6/M/75 Placebo</td>
<td>13</td>
<td>Betamethasone cream (-), acitretin (-), tacrolimus mouthwash (-), and antimalarial agent (-)</td>
<td>3</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>7/M/59 1% Pimecrolimus cream</td>
<td>2</td>
<td>Betamethasone cream (+)</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>8/F/78 Placebo</td>
<td>2</td>
<td>Cyclosporine mouthwashes (-)</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>9/M/49 Placebo</td>
<td>5</td>
<td>Betamethasone cream (-)</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>10/M/73 1% Pimecrolimus cream</td>
<td>5</td>
<td>Cyclosporine mouthwashes (-)</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>11/F/58 1% Pimecrolimus cream</td>
<td>3</td>
<td>Acriderm (-), tacrolimus mouthwash (-) and antimalarial agent (+)</td>
<td>3</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>12/F/78 Placebo</td>
<td>15</td>
<td>Betamethasone cream (-)</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviations: D0, day 0 (baseline); D14, day 14; D28, day 28; NA, data not available; +, moderate improvement; ++, important improvement; −, no improvement.

*The score range possible was from 0 to 4.
† The score range possible was from 0 to 12.
‡ Each blood sample was analyzed twice.
of treatment. No patient discontinued treatment for this reason. Blood pressure remained stable, and laboratory analyses demonstrated no abnormalities. To our knowledge, no toxicity data were available in humans before this study. Only pharmacological studies were performed by Novartis Pharma AG on animals (unpublished data, 2004). No toxic effects were found when this cream was applied on the mucosa of rabbits. To our knowledge, our study was the first to evaluate systemic exposure after mucosal exposure of pimecrolimus cream in humans. Blood concentrations of pimecrolimus were always above the threshold of detection and were higher (about 3 times) than those detected after use on skin.12 These results were predictable because the skin barrier is more efficient than the mucous barrier and because the treated lesions were erosive. In our study, blood levels of pimecrolimus seem not to be linked with the surface area of erosive lesions or the quantity of cream used, and an interindividual susceptibility can be suspected. Moreover, blood levels of pimecrolimus have not decreased with the healing of lesions. On the contrary, they have increased by D28 compared with D14. This slight increase could be because of the repeated exposures and/or a cumulative effect. The blood levels of pimecrolimus remain significantly below (about 10-fold lower) levels observed when treating psoriasis with oral pimecrolimus (ie, 54.5 ng/mL).13 However, even with blood levels of pimecrolimus superior to 50 ng/mL, no clinical, labora-
ory, renal function, or immunologic adverse effects were reported. Although the detection of low blood levels of pimecrolimus is reassuring, further controls on other patients and through a longer period should be performed to ensure that a significant amount of blood pimecrolimus is not detected and to rule out a cumulative effect.

To our knowledge, the best treatment of OELP remains high-potency topical corticosteroids.\textsuperscript{14,15} Depending on the series,\textsuperscript{16-19} they led to complete remission in 56% to 75% of patients. However, they are known to induce local atrophy, fragility, and telangiectasias, and to promote infections, including acute candidiasis. They also have theoretical risks of lowering local immunity and enhancing the development of malignancies. Few adverse effects have been reported when using topical calcineurin inhibitors for treating OELP. The most frequent is burning sensations. However, another concern when treating OELP with immunosuppressive drugs is the possible occurrence of neoplasia on chronic OELP lesions. Thus, possible carcinogenic effects of long-term use of topical calcineurin inhibitors in OELP also have to be considered. Topical corticosteroids offer long track records and are much less expensive than topical calcineurin inhibitors. Thus, until randomized comparative trials are available, topical calcineurin inhibitors should be used as a second-line therapy.

According to the present data, 1% pimecrolimus cream seems to be an effective and well-tolerated treatment for OELP. However, such treatment might be used for a long time because relapses occur rapidly when treatment is discontinued. Further studies on a larger population with long-term follow-up and monitoring of the blood level of pimecrolimus are required to better evaluate its usefulness and safety compared with other therapeutic modalities.

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Author Contributions: Dr Lacour had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Passeron, Lacour, Fontas, and Ortonne.

Acquisition of data: Passeron, Lacour, Fontas, and Ortonne.

Analysis and interpretation of data: Passeron, Lacour, and Fontas.

Drafting of the manuscript: Passeron.

Critical revision of the manuscript for important intellectual content: Lacour, Fontas, and Ortonne.

Statistical analysis: Fontas.

Obtained funding: Lacour.

Administrative, technical, and material support: Lacour and Ortonne.

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References


