Background: Chronic erosive oral lichen planus (EOLP) is a severe form of lichen of the buccal mucosa that is often resistant to systemic or topical therapies.

Objective: To evaluate the efficacy and safety of topical tacrolimus, 0.1 mg per 100 mL of water, in treating EOLP.

Design: Open-label, prospective, noncomparative study, with 6 months of treatment and 6 months of follow-up.

Setting: Dermatology department at a university hospital in Nice, France.

Patients: Ten patients with histologically proved EOLP that was refractory to treatment. Two patients were withdrawn because of noncompliance; findings in 8 were available for evaluation.

Interventions: Mouthwashes with tacrolimus, 0.1 mg per 100 mL of distilled water, 4 times daily for 6 months.

Main Outcome Measures: Efficacy was assessed using a calculated score that combined the intensity of spontaneous and meal-triggered pain and the surface area of erosions. Safety assessment included the monitoring of adverse effects, clinical laboratory values, and blood concentrations of tacrolimus.

Results: Among the 8 patients evaluated, 1 had no improvement and 7 were improved. The mean score decreased from 7.00 at baseline to 5.43 (a 22.43% decrease) at 1 month, 4.14 (a 40.86% decrease) at 2 months, 3.00 (a 57.14% decrease) at 3 months, 2.43 (a 65.29% decrease) at 4 months, 2.57 (a 63.29% decrease) at 5 months, and 3.43 (a 51.00% decrease) at 6 months. A decrease of symptoms was reported by the 7 responding patients as soon as the first month of treatment. No severe adverse effects were observed. All patients had whole-blood concentrations of tacrolimus below the detection limit of the assay (1.5 ng/mL) at all intervals. At 9 months, 6 patients had had a relapse within a mean of 38.6 days. At 12 months, all patients had had a relapse and required treatment with topical corticosteroids or systemic hydroxychloroquine sulfate.

Conclusion: Results of our study suggest a rapid and important palliating effect of low concentration of topical tacrolimus in distilled water in patients with EOLP.

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For these reasons, we sought to evaluate the efficacy and tolerability of topical tacrolimus, 0.1 mg per 100 mL of distilled water, in the treatment of EOLP.

PATIENTS AND METHODS

We conducted an open prospective study from January 1, 2000, to December 31, 2000. All patients gave written informed consent, and the study was approved by the local ethics committee. Enrolled patients had histologically proved EOLP that was refractory to treatment for more than 6 months. The symptoms were quantified using a calculated score based on the intensity of spontaneous and meal-triggered pain and the surface area of the erosions. 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; more than 15% to 25%, 3; and more than 25%, 4. The sum of the 3 items gave a maximal possible score of 12. A minimal score of 3 was necessary for inclusion. Neither topical nor systemic therapy with agents such as corticosteroids, retinoids, cyclosporine, griseofulvin, dapsone, or hydroxychloroquine sulfate was allowed during the study. All previous treatments for EOLP were stopped at least 4 weeks before the study. Patients were allowed to take acetaminophen in case of pain and topical amphotericin B in case of oral erosions. Because of the increased permeability of oral mucosa compared with skin and because of epithelial erosions, we chose a tacrolimus concentration of 0.1 mg per 100 mL of water, a lower concentration than that used for the treatment of atopic dermatitis. The topical medication was prepared by diluting one 0.5-mg capsule of tacrolimus (Prograf; Fujisawa Pharmaceutical Company, Ltd, Osaka, Japan) in 500 mL of distilled water. The medication was renewed every 4 weeks by a hospital pharmacist. We previously verified that this suspension would be stable for more than 1 month.

Four oral washes per day of 2 minutes each were performed during the first phase of the study, using 15 mL of the preparation. The daily frequency of oral rinses was subsequently modified on the basis of a clinical severity score. If the score decreased by at least 25% from the first visit, the number of daily mouthwashes was decreased by 1 in the subsequent period. On further decrease to less than 50% of the initial severity score, the number of daily mouthwashes was additionally decreased by 1. If there was no improvement at 2 consecutive visits, the number of daily mouthwashes was left unchanged. In cases of worsening, the number of daily mouthwashes was increased to the previous frequency.

The major criterion for efficacy was the clinical score, which was evaluated by the same investigator (V.O.) at baseline, after 2 weeks, and then monthly from the first (M1) to the sixth (M6) month of treatment. Investigators’ and patients’ global assessments were considered secondary outcomes. The duration of treatment was 6 months. Follow-up assessments were performed at 3 and 6 months (M9 and M12, respectively) after completion of treatment. The relationship between the score and the treatment duration was analyzed using the Spearman rank correlation coefficient.

Laboratory values (hematology, serum electrolytes, renal and hepatic function, and serum glucose level) were tested at baseline and repeated after 15 days and 1 month, and then monthly for the duration of the study. Clinical adverse effects were evaluated at all study intervals. To evaluate permucosal absorption of tacrolimus, monthly whole-blood concentrations were measured using a fluorescence polarization immunoassay (Abbott Laboratories; Abbott Park, Ill).

RESULTS

Ten patients with EOLP (6 women and 4 men) were included between January 1, 2000, and June 30, 2000. Two were withdrawn because of noncompliance; 8 patients were evaluated (mean age, 58.1 years [range, 34-74 years]). All patients had histologically proved, treatment-resistant EOLP, with a mean duration of 3.6 years (range, 6 months to 7 years). The mean baseline score was 7.00 (range, 3-10). One patient, who had leukoplastic lesions, showed no improvement after 2 months of treatment and was withdrawn from the study. Seven patients showed improvement. A decrease in symptoms was reported by the 7 responding patients as soon as the first month of treatment. Three of them were able to eat normally again at that time. The mean score decreased in parallel to 5.43 (a 22.43% decrease) at M1 (range, 5-8), 4.14 (a 40.86% decrease) at M2 (range, 3-5), 3.00 (a 57.14% decrease) at M3 (range, 1-5), 2.43 (a 65.29% decrease) at M4 (range, 1-5), 2.57 (a 63.29% decrease) at M5 (range, 0-6), and 3.43 (a 51.00% decrease) at M6 (range, 0-6) (Figure 1 and Figure 2). This improvement allowed a progressive subsequent decrease in the number of daily mouthwashes. Three patients were able to stop treatment completely at M5. However, relapse occurred after cessation of the mouthwashes. Although the scores of treated patients continued to improve from M5 to M6, the scores of the 3 who had discontinued treat-
ointment could be a safe, effective, and well-tolerated therapy. Results in this patient also suggested that topical tacrolimus (Table). No adverse effects were observed. Three patients complained of tingling immediately after treatment, lasting less than 1 hour. Two also reported oral dryness. One patient had a recurrence of labial herpes during the treatment that was similar to his previous episodes and not suggestive of a drug-related effect. No patient experienced oral candidiasis. No biological adverse effects were recorded. All patients had whole-blood concentrations of tacrolimus below the detection limit of the assay (1.5 ng/mL) at all intervals.

The 7 patients were examined 3 and 6 months (at M9 and M12, respectively) after the end of treatment. At M9, 6 patients had relapsed within a mean of 38.6 days (range, 7 to 90 days); their mean score was 4.00 (range, 1-8). At M12, all patients had had a relapse of EOLP and required treatment with topical corticosteroids or systemic hydroxychloroquine. Whereas the patients were resistant to usual treatments for EOLP before starting tacrolimus therapy, they responded well when treated again with topical or systemic therapy. At M12, their mean score was 2.71 (range, 0-6).

The results of our study demonstrate that topical tacrolimus at a concentration of 0.1 mg per 100 mL of distilled water has a rapid and significant effect in patients with EOLP that is refractory to other therapies. Among 8 patients, a single failure of treatment was observed in a patient who had a particularly leukoplakic form of oral lichen planus, perhaps due to decreased absorption of tacrolimus over the hyperplastic mucosa. The efficacy of tacrolimus in EOLP, which is considered to have a T-cell–mediated pathogenesis, may be due to its inhibitory effect on the activation and proliferation of T lymphocytes. To our knowledge, few studies have assessed the therapeutic effect of topical tacrolimus in EOLP. In the first observational series, the possible efficacy of 0.1% tacrolimus was shown in 4 patients. In the same study, 2 additional patients were treated for vulvar erosive lichen planus. In that study, tacrolimus was used twice daily in a hydrophilic petrolatum ointment. In another case report, 0.1% tacrolimus in a formulation base (white petrolatum, mineral oil, propylene carbonate, white wax, and paraffin) was used; the results in this patient also suggested that topical tacrolimus ointment could be safe, effective, and well-tolerated therapeutic modality. Subsequently, 2 open studies were published, one of which was a retrospective study of 13 patients with EOLP. Those patients were treated with various concentrations (0.03%, 0.1%, or 0.3%) of tacrolimus in a bland ointment base, 2, 3, or 4 times daily. Eleven patients had a symptomatic response to treatment that was partial in 8 cases and complete in 3. Flares occurred soon after stopping the treatment. The other study was an open-label, noncomparative study of 0.1% tacrolimus in a paraffin ointment base, administered twice daily. Tacrolimus therapy caused a statistically significant improvement of symptoms within 1 week of commencement of therapy. In that study, 13 of 17 patients had a relapse within 2 to 15 weeks of cessation of tacrolimus therapy. We chose to use a tacrolimus suspension in distilled water because of its simple formulation and because patients find mouthwashes to be more convenient and less uncomfortable than applying ointment in the mouth.

In our study, no severe drug-related adverse effects were observed. The sensation of mouth burning or dryness was observed in less than half of the patients and was transient, resolving as EOLP improved. Blood concentrations of tacrolimus were monitored in only 1 previous study, in which tacrolimus levels were within the therapeutic range in 8 of 17 patients who were observed after systemic administration. Despite mucosal erosions and subsequent compromised barrier function, no systemic exposure to tacrolimus could be detected in our study. This finding was likely due to the low concentration of tacrolimus we used. The efficacy of such a low dose is an important finding, since the long-term effects of topical immunosuppressants, particularly the risks of skin cancer facilitation, are still unknown. Chronic EOLP carries a risk of oral cancer independently, which suggests that minimizing immunosuppressive effects should be considered.

A relapse of erosive lesions was observed in all of our patients a few days to months after discontinuation of treatment, suggesting that tacrolimus has a purely palliative and not a curative effect. However, an alternate-day or intermittent treatment could probably be used on a long-term basis, with minimal discomfort and adverse effects for the patients. Furthermore, whereas EOLP in our patients was refractory to usual treatments before starting tacrolimus therapy, their EOLP responded well to topical corticosteroids (6 patients) or to hydroxychloroquine therapy (1 patient) when these patients relapsed at the end of the study. This finding suggests that short-pulse treatment with topical tacrolimus could be sufficient in some cases to improve symptoms in case of resistance to conventional drugs.

There could be some bias in our trial, which was an uncontrolled study and included a small number of patients. However, our study was prospective, with stringent inclusion criteria and objective, scored evaluation of the results, in contrast to studies that use imprecise trial methods and to observational series of patients with EOLP that are not prospective. Furthermore, spontaneous remission of oral lichen planus is rare, particularly when it is in the erosive form. A large randomized, controlled, double-blinded trial that compares topical tacrolimus with a reference treatment such as topical corti-

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costeroids and includes a quality-of-life study is needed to confirm our results.

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