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CLINICAL REPORT

A Comparison of Treatment of Oral Lichen Planus with Topical Tacrolimus and Triamcinolone Acetonide Ointment

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Treatment of symptomatic oral lichen planus remains a challenging problem. This study compared the efficacy of topical tacrolimus ointment with triamcinolone acetonide ointment in patients with oral lichen planus. Twenty patients (group I) were treated with topical tacrolimus 0.1% ointment 4 times daily, and 20 (group II) were treated with triamcinolone acetonide 0.1% ointment 4 times daily. The clinical effect was graded after 6 weeks. In group I, 6 patients healed, 12 showed improvement and 2 showed no improvement. In group II, 2 patients healed, 7 improved and 11 showed no improvement. The most commonly reported side-effect in both groups was temporary burning or stinging at the site of application. Unfortunately, oral lesions recurred within 3–9 weeks of cessation of treatment in 13 of the 18 patients who had initially shown an improvement or were healed in group I and in 7 of the 9 patients in group II. Topical tacrolimus 0.1% ointment induced a better initial therapeutic response than triamcinolone acetonide 0.1% ointment. However, relapses occurred frequently within 3–9 weeks of the cessation of treatment. ***Key words: side-effects; treatment.***

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Oral lichen planus (OLP) is a common benign inflammatory disease affecting mainly middle-aged and elderly people, with a prevalence of approximately 0.5–2%. The disease has a female:male ratio of approximately 2:1 and may persist for many years (1). The diagnosis of OLP is based on a combination of characteristic clinical findings, history and histopathological examination. The hyperkeratotic (white) variant of OLP is often symptomless. The atrophic or the erythematous (red) variant and the erosive or the ulcerative (yellow) variants of OLP generally have persistent symptoms (1–5).

Treatment of symptomatic OLP is challenging. Several drugs have been used with varying efficacy (1, 3). Specific treatment includes corticosteroids (topical, intralesional or systemic), retinoids, cyclosporine, psoralen plus ultraviolet A light (PUVA), griseofulvin, hydroxychloroquine and dapsone (1, 3).

Recently, topical tacrolimus was reported to be effective in the treatment of patients with OLP in a number of pilot studies (2–6). However, these studies lacked adequate control groups, and relapses of symptomatic OLP were also reported to occur frequently, generally within weeks of the cessation of topical tacrolimus treatment (2–6).The aim of this prospective randomized study was to compare the efficacy of topical tacrolimus 0.1% ointment with that of triamcinolone acetonide 0.1% ointment in patients with symptomatic OLP. The side-effects of the treatment in each group and the periods of remission after the cessation of therapy were also compared.

MATERIALS AND METHODS

A prospective randomized study was conducted between 2001 and 2004 in 40 Caucasian patients (30 women, 10 men; age range 32–82 years; mean 58 years) with a confirmed diagnosis of symptomatic OLP based on clinical and histopathological features at the department of Dermatology of the Albert Schweitzer Hospital, Dordrecht, The Netherlands. Exclusion criteria were: age younger than 18 years; histopathological examination with atypical or lichenoid dysplastic features; asymptomatic oral lesions and specific treatment within 4 weeks prior to the study. The extent and the severity of OLP and the prior treatment schedules in the 40 recruited patients were comparable and showed no statistically significant difference ($p > 0.99$). All patients were treated for 6 weeks. Treatment was discontinued earlier when patients showed a complete healing. The follow-up period was for at least 3 months. Treatments were randomly allocated to patients in order of inclusion according to a predetermined randomization-list stratified by sex. The patients were divided into two groups. Each patient was provided with detailed verbal and written information on the study protocol. Each patient provided written informed consent to participate in the study. Ethical approval was obtained prior to commencing the study.

In group I, 20 patients were treated with topical tacrolimus 0.1% ointment (Protopic® 0.1%, Astellas Pharma Inc., The Netherlands), which was applied 4 times a day onto the symptomatic oral lesions. In group II, 20 patients were treated with triamcinolone acetonide 0.1% in hypromellose 20% ointment, which was also applied 4 times a day. The reasons for this administration schedule in both groups were to achieve a comparable level of patient compliance and to achieve effective numbers of application of the ointments because topical agents do not easily adhere to the moist mucous membranes.

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The clinical effect of treatment in the patients was graded after 6 weeks by the treating physician using an ordinal score and recorded as worse, unchanged, improved or healed. The ordinal (ranked) scoring involved assessing the severity and the extent of the disease. An improvement of less than 30% in the extent and the severity of the lesion was scored as unchanged. An improvement of more than 30% in the extent and the severity of the lesions was scored as improved and as healed when the lesion had resolved completely. No blood samples were taken for determining the levels of tacrolimus and cortisol.

Statistical analysis

Statistical analysis of the results was performed by means of the exact χ^2 trend test and the Fisher's exact test with a statistical significance set at $p < 0.05$.

RESULTS

The patients' characteristics and results are shown in Table I. One patient in group I had vulvovaginal-gingival syndrome. The two groups were similar for characteristics such as sex, age, symptoms and the duration of the disease, histopathology, the predominant form of OLP and the involved anatomical site. The initial results of the treatment in group I were better than in group II (exact χ^2 trend test: $p = 0.007$). Side-effects were temporary and more common in group I, but the difference was not statistically significant (Fisher's exact test: $p = 0.16$). The most frequent side-effect was transient irritation including burning or stinging at the site of application lasting for about 10–30 min. It occurred primarily in patients with the erosive or ulcerative form of OLP in both groups, but it did not lead to discontinuation of the treatment in any patient. Moreover, the local irritation after treatment was significantly reduced, when the lesions became less erosive or ulcerative. Unfortunately, oral lesions recurred within 3–9 weeks (mean 5 weeks) after the cessation of the treatment in 13 (72%) of the 18 patients in group I and in 7 (78%) of the 9 patients in group II, who initially showed improvement or healing.

Table I. *Treatment with topical tacrolimus 0.1% ointment and triamcinolone acetonide 0.1% ointment in 40 patients with symptomatic oral lichen planus (OLP)*

Patients	Group I (tacrolimus)	Group II (triamcinolone)
Women/men	15/5	15/5
Age, mean (range) (years)	57 (32–82)	58 (36–78)
Duration of OLP, mean (range) (years)	3 (0.5–7)	3.5 (0.5–8)
Symptoms		
Pain	16	15
Buccal mucosa	10	11
Extra-oral LP	1 vulva	1 cutaneous
Histopathology, n (%)		
OLP	13 (65)	12 (60)
Compatible with OLP	7 (35)	8 (40)
Predominant form, n (%)		
Erosive/ulcerative	14 (70)	15 (75)
Atrophic/erythematous	4 (20)	3 (15)
Hyperkeratotic	2 (10)	2 (10)
Affected site of OLP		
Buccal mucosa	16	17
Tongue	8	8
Gingiva	10	8
Results after ≤ 6 weeks of treatment, n (%)		
Healing	6 (30)	2 (10)
Improvement	12 (60)	7 (35)
No improvement	2 (10)	11 (55)
Worse	–	–
Side-effects, n (%)	8 (40)	3 (15)
Follow-up, mean (range) (months)	15 (3–24)	14 (3–24)

DISCUSSION

Tacrolimus is an immunosuppressive macrolide drug produced by *Streptomyces tsukubaensis* and used to prevent transplant rejection (2, 7). *In vitro*, tacrolimus exerts an activity that is 10–100 times higher than that of cyclosporine (2). Topical tacrolimus (FK 506, Protopic® 0.1% or 0.03% ointment) was approved as a safe treatment for atopic dermatitis (4). Tacrolimus is a smaller molecule and penetrates better into the skin and the mucosa than cyclosporine (2, 3). Generally, no systemic blood levels of tacrolimus were detected in most patients with OLP (2, 4). However, systemic absorption of tacrolimus may occur with low, but measurable, blood levels through absorption via the oral mucosa or ingestion (6, 8). A contributing therapeutic systemic effect cannot be excluded with certainty in such cases (8). Side-effects such as burning sensation at the site of application, transient taste disturbance, intermittent headaches, and rarely patchy hyperpigmentation of the oral mucosa as a result of topical tacrolimus treatment in OLP were reported (2, 4, 5, 8, 9). Although its exact mechanism of action in OLP remains unknown, topical tacrolimus was shown to inhibit T-lymphocyte activation by inhibiting the phosphatase activity of calcineurin. Without calcineurin to dephosphorylate the nuclear factor of activated T cells, gene transcription for lymphokines, IL-2, and interferon-γ is inhibited leading to a decrease in the number of lymphocytes (3, 7). Recently, topical tacrolimus was also reported to be a safe and effective treatment in vulvar lichen planus (7).

The results of this study allow the conclusion that treatment with topical tacrolimus 0.1% ointment four times daily induced a better initial therapeutic response than triamcinolone acetonide 0.1% ointment in patients with symptomatic OLP. However, relapses occurred frequently in both groups within several weeks after the cessation of both the treatments. Transient irritation at the site of application was more common in patients treated with topical tacrolimus, but did not lead to discontinuation of the treatment. It is noteworthy that

in this study, tacrolimus was applied 4 times daily, because topical agents adhere poorly to the moist mucous membranes (10).

Prolonged or intermittent use of topical tacrolimus ointment in patients with symptomatic OLP may be useful, but remains to be clearly established in large, well-designed clinical studies. Nonetheless, at present, topical tacrolimus may be a valuable addition to the already existing therapeutic modalities for treating patients with OLP.

There was no conflict of interest.

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