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A randomized-controlled trial to compare topical cyclosporin with triamcinolone acetonide for the treatment of oral lichen planus

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BACKGROUND: Various treatments have been employed to treat symptomatic oral lichen planus (OLP), but a complete cure is very difficult to achieve because of its recalcitrant nature. Topical cyclosporin therapy of OLP has shown conflicting results in many reports. The purpose of this study was to compare the effectiveness of cyclosporin solution with triamcinolone acetonide 0.1% in orabase in the treatment of Thai patients with OLP.

METHODS: Thirteen Thai patients with symptomatic OLP and proven by biopsy were randomly assigned treatment with cyclosporin (six) or triamcinolone acetonide 0.1% (seven). The patients were instructed to apply cyclosporin or triamcinolone acetonide 0.1% three times daily at the marker lesions and affected areas. The assessments were at weeks 0, 2, 4, 8 by clinical scoring and grid measurement of the target lesions. Cyclosporin levels were assessed at weeks 2 and 8 of treatment. Pain and burning sensation were evaluated by linear visual analogue scale (0–10).

RESULTS: OLP patients in the triamcinolone acetonide group showed equal cases of clinical complete and partial remission (50%). Whereas, in the cyclosporin group, there was partial remission in only two cases (33.5%) and no response in four cases (66.7%). However, our study showed that there were no statistical differences in pain, burning sensation and clinical response in OLP patients between the two groups ($P > 0.01$). Moreover, five of six cases in the cyclosporin group developed side-effects such as transient burning sensation, itching, swelling lips, petechial haemorrhages and others.

CONCLUSION: Our results indicated that topical cyclosporin did not provide any beneficial effect and was not more effective than triamcinolone acetonide 0.1% in the treatment of Thai patients with symptomatic OLP.
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Keywords: cyclosporin; oral lichen planus; triamcinolone acetonide

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Introduction

Oral lichen planus (OLP) is a common chronic inflammatory disease of oral mucosa and skin in which the immunopathogenesis involving T cell-mediated cytotoxicity (1). The oral lesions in atrophic-erosive form of OLP can cause symptoms ranging from burning sensation to severe pain, interfering with speaking, eating and swallowing (2, 3). Thus, symptomatic OLP patients often require therapy to reduce pain and burning sensation (4). During the past decade, various treatments have been used to treat symptomatic OLP, but a complete cure has not yet been accomplished because of its recalcitrants nature. Topical steroids are widely used in the treatment of OLP to reduce pain and inflammation. Many studies have reported on the effectiveness of topical cyclosporin but conflicting results also exist in many documents.

Cyclosporin is an immunosuppressant which inhibits the gene transcription of IL-1, IL-2, IFN-γ and other factors produced by antigen-stimulated T cells, thereby suppressing T-cell cytokines (5, 6). Some studies have reported that cyclosporin is effective (7–10). However, some authors have reported little benefit (11) or no significant improvement (12). However, comparative study of cyclosporin and triamcinolone acetonide 0.1% orabase in the treatment of OLP has not shown significant difference of remission (13). Recently, a randomized-controlled trial of the comparison of the effectiveness of cyclosporin and clobetasol in the topical

management of OLP in one study has shown that clobetasol is more effective than cyclosporin in inducing clinical improvement (14). Therefore, topical cyclosporin therapy of OLP has shown conflicting results. The purpose of our study was to compare the effectiveness of cyclosporin solution with triamcinolone acetonide 0.1% in orabase in the treatment of Thai patients with OLP.

Materials and methods

Patients

Thirteen Thai patients (10 females, three males; age range: 22–69 years; mean ± SD: 46.38 ± 13.09) with symptomatic OLP from Oral Medicine Clinic, Faculty of Dentistry, Chulalongkorn University; Dental Division and Saraburi Hospital were enrolled in this study. The inclusion criteria by Asian Lichen Planus Group (15) are as follows:

1 all patients had clinically and histologically confirmed OLP by WHO criteria (16);
2 patients receiving topical or systemic medication for OLP were included in this trial only after a wash-out period of 2–4 weeks, respectively and
3 patients with secondary infection of the OLP lesions were first treated with antimicrobials and chlorhexidine mouthrinse.

The exclusion criteria are as follows:

1 they had been treated previously by either of the trial medications and had worsened during the treatment and
2 systemic diseases such as hypertension, serious or recurrent infections, respiratory, renal or heart disease, recent history of malignancy, insulin-dependent diabetes mellitus, active peptic ulcers, gastrointestinal disease or pregnancy.

Verbal and written informed consent were obtained from all patients with OLP before conducting the study.

Study design and treatment

OLP patients were randomly assigned to receive triamcinolone acetonide 0.1% orabase or cyclosporin solution by sealed envelopes. They were instructed to apply cyclosporin (Sandimmun Neoral® 100 mg/ml; Novartis Pharma S.A., France for Novartis Pharma AG, Basle, Switzerland) or triamcinolone acetonide 0.1% orabase (Bristol Myers, Squibb) on the dried lesions three times daily after meals, for a period of 8 weeks. The patients were informed not to drink, eat or smoke for 30 min after application. Complete blood counts and blood pressure at baseline, week 2 and week 8 were assessed in cyclosporin group. Whole blood cyclosporin levels were assessed at weeks 2 and 8 of treatment. During treatment, the patients were asked to report immediately if there were any side-effects from the application of cyclosporin. If the toxicity or adverse effects persisted, the number of applications was reduced or the patients were referred to the clinician and then they were excluded from the study.

Patient assessment

During treatment, the patients were assessed at weeks 0, 2, 4, 8 and follow up after 12 and then every 3 months for 1 year. In all patients, the site of lesions was recorded and the most severe area was identified as the marker lesion. By oral examination, the criteria scale of Thongprasom et al. (17) were used as follows: 0 = no lesion/normal mucosa; 1 = mild white striae/no erythematous area; 2 = white striae with atrophic area <1 cm^2; 3 = white striae with atrophic area >1 cm^2; 4 = white striae with erosive area <1 cm^2; 5 = white striae with erosive area >1 cm^2.

Moreover, the lesion was measured by a transparent grid calibrated to 2 mm^2 to confirm the scores. Pain and burning sensation were recorded by patients using visual analogue scale (VAS) on 0–100 mm (18).

Clinical evaluation of the OLP lesions after treatment at week 8 were graded by Asian Lichen planus Group as follows: Grade 1, clearance of lesion (normal mucosa); Grade 2, complete remission (CR; reticular with no symptoms); Grade 3, partial remission (improvement of lesion and/or symptom); Grade 4, no improvement; Grade 5, condition worsened.

To evaluate our results, CR were grades 1 and 2 while no remission were grades 4 and 5.

Statistical analysis

Mann–Whitney Test was used to analyse for pain and burning sensation in the two groups. Chi-square test was analysed the clinical scores and compared the clinical responses between the two groups. $P < 0.05$ was considered to be statistically significant.

Results

Fourteen patients with OLP were enrolled at the beginning of this study but the trial no. 5 was invalid randomization, so this patient was excluded from trial. Eleven of the buccal mucosa areas were the most marker lesions while labial mucosa were used in two cases. The clinical characteristics of OLP patients are shown in Table 1. The comparison of clinical response in cyclosporin and triamcinolone acetonide 0.1% groups at week 8 was presented in Table 2. Clinical scoring in both groups were also illustrated in Fig. 1. However, there was no statistical difference in clinical response between the two groups ($P > 0.01$). There was no statistical significance in burning sensation between the two groups ($P > 0.01$). VAS pain and burning sensation of the patients in the treatment groups were illustrated in Figs 2 and 3. Cyclosporin levels at week 2 showed 228.04 ng/ml in one case while the others were <25 ng/ml. At week 8, cyclosporin levels in all six cases were ranged from 6.13 to <25 ng/ml which was within normal limits. The side-effects of the subjects who applied topical cyclosporin were transient burning sensation (four), gastrointestinal discomfort (one), breast tenderness (one), dizziness (one), itching (one), swelling lips (one) and petechial haemorrhages (one) and were reported in Table 3. Four cases in the cyclosporin group developed transient burning sensation after

Table 1 Characteristics of OLP patients and treatment evaluation at week 8 in cyclosporin and triamcinolone acetonide groups

Number	*Age (years)*	*Sex*	*Site*	*Treatment*	*Week 8 response (grade)*
4001	52	F	Buccal mucosa	C	PR (3)
4002	38	F	Buccal mucosa	C	NR (4)
4003	47	M	Buccal mucosa	S	CR (2)
4004	62	M	Buccal mucosa	S	PR (3)
4005	46	F	Buccal mucosa	Invalid randomization	–
4006	22	F	Buccal mucosa	S	PR (3)
4007	39	F	Buccal mucosa	C	NR (4)
4008	52	F	Buccal mucosa	C	NR (5)
4009	69	F	Buccal mucosa	S	CR (2)
4010	55	F	Buccal mucosa	S	CR (1)
4011	56	F	Labial mucosa	S	PR (3)
4012	30	F	Buccal mucosa	C	PR (3)
4013	38	F	Labial and buccal mucosa	C	NR (5)
4014	43	M	Buccal mucosa	S	–[a]

C, cyclosporin; S, steroid (triamcinolone acetonide 0.1%); CR, complete remission; PR, partial remission; NR, no response; OLP, oral lichen planus.
[a]Missed follow up.

Table 2 Comparative clinical evaluation in OLP patients treated with cyclosporin and triamcinolone acetonide groups at week 8

	Clinical response (cases %)	
Group	*CR*	*PR/NR*
Cyclosporin	–	2 (33.5%)/4 (66.7%)
Triamcinolone acetonide[a]	3 (50%)	3 (50%)
Total	3	9

[a]One patient missed follow up at week 8.
OLP, oral lichen planus; CR, complete remission; PR, partial remission; NR, no response.

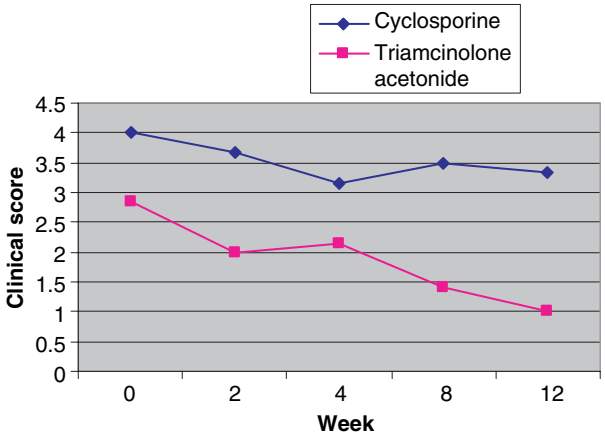

Figure 1 Clinical scoring of oral lichen planus (OLP) patients at weeks 0, 2, 4 and 8 in OLP patients treated with cyclosporin and triamcinolone acetonide groups.

applying medication. Petechial haemorrhages were found at the soft palate in one case at week 8; however, her platelet count was 181 100 cell/mm^3 which was

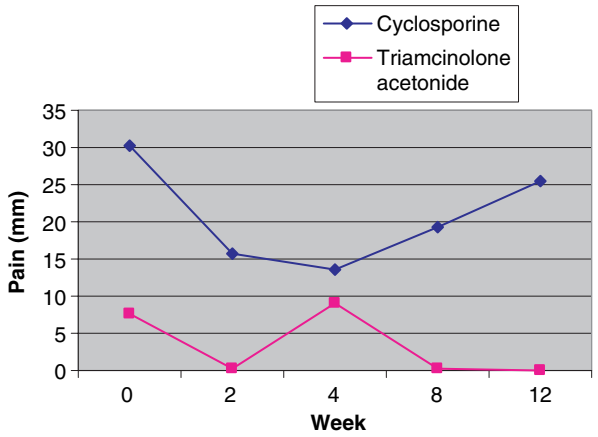

Figure 2 Visual analogue scale recording of pain in oral lichen planus patients treated with cyclosporin and triamcinolone acetonide groups.

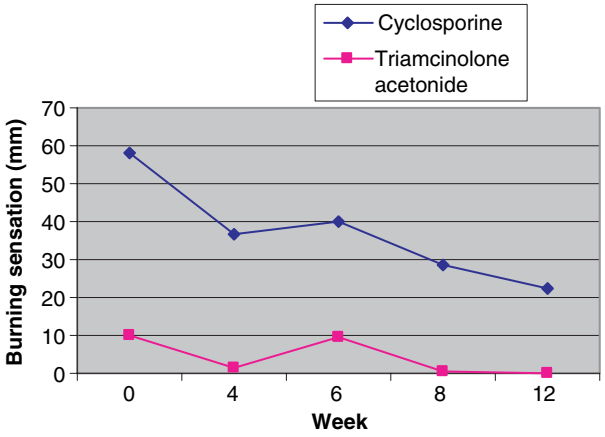

Figure 3 Visual analogue scale recording of burning sensation in oral lichen planus patients treated with cyclosporin and triamcinolone acetonide groups.

within normal limits. No side-effects were reported from the subjects in the triamcinolone acetonide group.

Discussion

Although the number of OLP patients in this study was only 13 cases, this is not unlike other studies (4, 7, 8, 13, 19, 20). It is a known fact that the number of female patients with OLP is more than males as shown in previous reports and our present study (14, 21, 22–24).

The transparent grid, the intra-oral grid was found to be useful for the objective measurement of OLP lesions especially for ulcerations and erythematous areas. This method should be used together with clinical scoring to double-check and confirm the accurate measurement at the marker areas. From our experiences, the white striae were difficult to copy and measure from the lesional areas because the striae were not in a linear pattern.

Pain in OLP patients treated with cyclosporin after week 4 was higher than the triamcinolone acetonide group. However, there was one case in the triamcinolone acetonide group who missed follow up after week 3

Table 3 Characteristics of oral lichen planus patients in cyclosporin group, cyclosporin levels at weeks 2, 8 and side-effects

Number	Age (year)	Sex	Cyclosporin levels (ng/ml)[a] Week 2	Week 8	Side-effects
4001	52	F	<25	6.13	Sore throat (week 8)
4002	38	F	<25	9.15	Gastrointestinal discomfort, breast tenderness, petechial haemorrhages, purpura (week 8) Burning sensation (week 12)
4007	39	F	<25	<25	None
4008	52	F	–	<25	Dizziness (week 4) Transient burning sensation (weeks 4 and 8)
4012	30	F	228.04	<25	Transient burning sensation (week 8)
4013	38	F	<25	<25	Transient burning sensation, itching, lips swelling (week 2)

[a]Normal cyclosporin level (<150 ng/ml) value at Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

because of severe pain. There was no statistical significance in burning sensation between the two groups ($P > 0.01$). According to the clinical scoring, there were no statistically significant differences between the two groups ($P > 0.01$).

One case in the cyclosporin group showed high blood cyclosporin level at week 2, so we instructed the patient to reduce the frequency of drug application to twice daily. However, for patient safety and monitoring reasons, we repeated the blood cyclosporin test at week 3 which showed the blood cyclosporin level at <25 ng/ml. In our study, blood cyclosporin levels in all cases showed low levels at week 2, except in one case that showed high cyclosporin levels. At the end point of therapy in week 8, all OLP patients showed cyclosporin levels to be within normal limit. Transient burning sensation, gastrointestinal discomfort, breast tenderness, dizziness, itching, swelling lips and petechial haemorrhages were reported from most of the subjects in the cyclosporin group after application of the medication. One case developed petechial haemorrhages on the soft palate at week 8; however, her platelet count was 181 100 cell/mm^3. Interestingly, only one case had no side-effect from cyclosporin application. However, no serious systemic side-effects were found in all OLP patients in this study. In the triamcinolone acetonide group, six cases had no side-effects while one case #4013 had got more severe pain and worsening of the lesions after treatment. Thus, he failed to follow up at week 3.

All six cases in the cyclosporin group showed partial response to the treatment, this indicated that cyclosporin might not inhibit cytokines in the OLP lesions directly or indirectly. Interestingly, it has been reported that cytokine TNF-α may be involved in the immunopathogenesis in Thai patients with symptomatic OLP (25). Because cyclosporin is an immunosuppressant which inhibits the gene transcription of IL-1, IL-2, IFN-γ and other factors produced by antigen-stimulated T cells, thereby suppressing T-cell cytokines, it might not inhibit TNF-α or mildly inhibit this cytokine in OLP lesions of Thai patients.

During the follow up of OLP patients in both groups for 12 months after treatment, neither patients in the cyclosporin nor triamcinolone acetonide groups showed improvement of the lesions. As OLP is a chronic inflammatory disease and recalcitrant in nature, our results agreed and confirmed with the previous study of Sieg et al. (13) that complete resolution of the OLP lesions did not occur in any patient.

Furthermore, a recent study has shown that topical steroid (clobetasol) is more effective than cyclosporin in inducing clinical improvement in atrophic-erosive OLP (14). This study was a high standard double-blind, randomized-controlled trial in the treatment of symptomatic OLP that reported clinical assessments, adverse effects, cost-effectiveness and completely follow up. In our opinion, we support this study that topical steroid is recommended as the first-line therapy for patients with symptomatic OLP because of minimal side-effects and cost–benefit in long-term treatment. Whereas topical cyclosporin could be used as a second-line therapy.

Although the number of our patients was small, the results of this study indicated that topical cyclosporin did not seem to be effective in the treatment of symptomatic OLP in Thai patients. In conclusion, our results confirm that topical cyclosporin is not more effective than triamcinolone acetonide 0.1%. Therefore, topical cyclosporin can be used as an alternative treatment of recalcitrant OLP but it cannot be considered as the first drug of choice because of the high cost in the long-term treatment.

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