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Short-term clinical evaluation of intralesional triamcinolone acetonide injection for ulcerative oral lichen planus

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BACKGROUND: Efforts are made in a continued searching for novel therapies for symptomatic oral lichen planus (OLP). This study aimed to evaluate the efficacy and safety of intralesional triamcinolone acetonide (TA) injection for ulcerative OLP.

METHODS: Forty-five patients with clinical and histologically confirmed ulcerative OLP on bilateral buccal mucosa, one for treatment and the other for control, were studied. All participants received 0.5 ml TA (40 mg/ml) on experimental sites. Visual analogue scale score and lesion areas were recorded at the time of injection and 1-week interval. After 2 weeks, if the treated ulceration reduced <81% in size, a second injection was given.

RESULTS: The treated group gave rapid relief of signs and symptoms, while the control group showed minimal decrease. 38 (84.4%) patients demonstrated complete response in ulceration size. No complications were noted with TA injections.

CONCLUSIONS: Intralesional TA injection in ulcerative OLP is effective and safe in achieving lesion and pain regression.

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Introduction

Oral lichen planus (OLP), most frequently involving buccal mucosa symmetrically, is a common chronic inflammatory disease of unknown aetiology, affecting 0.1–4% of various populations (1, 2). Recently, the classification of OLP tends to be simplified into three major clinical forms (reticular/hyperkeratotic, erythematous/erosive and ulcerative), which could alternate and overlap in a dynamic state as disease progress (3–5). Reticular lesions present as white lines, plaque or papules, characterized by Wickham' striae. Reticular OLP occurs most frequently, but usually is asymptomatic and thus requires no treatment. Erythematous (erosive) form is clinically defined as an area of mucosal erythema caused by inflammation or epithelial thinning, or both. Frequently, erythematous lesions are often associated with burning pain and sensitivity. An ulcerative area is presented as yellow/white sloughed inflammatory necrotic tissue secondary to a break in the continuity of the mucosal epithelium with erythema and white striations on the periphery. Ulceration is the most severe form and always painful that interferes with eating, speech and swallowing (3–5).

Many treatment regimens have been attempted in management of ulcerative OLP to resolve clinical symptoms and signs (6). Topical steroids remain as mainstay of treatment and might be made in ointment, mouthwash, spray or paste (7–11). However, some lesions are not responsive or responsive slowly to those topical steroids, making patients suffer for a long time (7–9). Effective delivery of steroids to affected mucosal sites could still be problematic. Intralesional steroid is suggested as an effective and simple modality with the aim of achieving sufficiently high drug concentration locally for enhanced immunosuppressing effect while limiting systemic toxicity (12, 13). Intralesional triamcinolone acetonide (TA) injection has been reported in successful treatment of oral submucous fibrosis (13, 14), temporomandibular joint osteoarthrosis (15), central giant cell granuloma (16–18) and cheilitis granulomatosa (19). However, there is limited experience with intralesional administration of TA in management of ulcerative OLP and no control study has been carried out to exclude spontaneous remission of disease (20, 21).

Recently, though various scoring systems have been used for monitoring OLP activity as disease evolves and resolves, no one is widely accepted. Table 1 showed a semiquantitative REU (reticular, erosive and ulcerative lesion) scoring system proposed recently by

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Table 1 The REU scoring system for oral lichen planus[a]

Clinical form	*Scoring*
Reticular/hyperkeratotic	0 = no white striations; 1 = presence of white striations or keratotic papules
Erosive/erythematous	0 = no lesion; 1 = lesions <100 mm^2; 2 = lesions from 100 to 300 mm^2; 3 = lesions >300 mm^2
Ulcerative	0 = no lesion; 1 = lesions <100 mm^2; 2 = lesions from 100 to 300 mm^2; 3 = lesions >300 mm^2
Total[b]	$\sum R + \sum (E \times 1.5) + \sum (U \times 2.0)$

[a]Piboonniyom et al. (3).
[b]The oral cavity of each individual was divided into 10 sites: upper/lower labial mucosa, right buccal mucosa, left buccal mucosa, dorsal tongue, ventral tongue, floor of mouth, hard palate mucosa, soft palate/tonsillar pillars, maxillary gingiva and mandibular gingival. The total score was derived by summation of the scores of all 10 areas multiplied by a weighted factor of 1.5 (erythematous lesion) or 2.0 (ulcerative lesion).

Piboonniyom et al. (3), which seemed easy to use, gave good interexaminer consistency and correlated well with the clinical findings of healing, but the REU score needs further evidence in a larger cohort of patients.

The purpose of the present study was to evaluate the safety and clinical efficacy of intralesional TA injection upon resolving signs and symptoms for ulcerative OLP, together with the practicability of the REU scale.

Materials and methods

Patient group

This was a controlled, short-term study. Patients with clinical and histopathological proven ulcerative OLP were considered for inclusion in our study at the Department of Oral Medicine, Hospital of Stomatology, Sun Yat-sen University. Moreover, inclusion criteria included ulcerative lesion on bilateral buccal mucosa. Every patient enrolled was given a number in turn. When it was an odd number, lesion on right buccal mucosa was allocated to the control group (where no therapeutic measurement was given at the first 2 weeks) and if an even number, lesion on the right was in the experiment group (where TA injection was administered). That is to say, lesions on the right and left buccal mucosa would receive different management and be evaluated separately as one independent object for a self-controlled trial. Individuals would be excluded if they suffered from other local or systemic disease, were pregnant or on lactation period, could not finish the follow-up review for social or personal reasons. Patients who had taken immunodepressant or immunopotentiating drugs during the previous 1 month were also excluded. At the initial visit, some data were documented, including age, gender, medical history, drug history and symptoms. Informed consent to participate in this study was obtained from all patients after both verbal and written study explanations. Protocol was submitted and approved by our Institutional Review Board (IRB).

Clinical assessment

Evaluation of clinical signs and symptoms, as well as a questionnaire documenting potential adverse effects were completed at each visit. The three principle parameters, evaluated in patients by two clinicians with good interexaminer consistency, were pain, and surface areas of erythematous and ulcerative lesions. To score symptomatic severity (subjective score), the visual analogue scale (VAS) was used as a self-administered assessment. Patients were instructed to bisect a 100-mm line from 0 (no pain) to 100 (extreme pain) at a point appropriate to rank present discomfort at moment when their ulcerative lesion was brushed gently with a tampon. Surface areas of erythema and ulceration were measured with a sterile flexible periodontal scale probe, and were estimated in squared millimetres. In addition, clinical appearance of lesions was also valued by REU score (Table 1). REU of the right/left buccal lesion was calculated according to the following formula: $R + E \times 1.5 + U \times 2.0$, irrespective of lesions on other oral sites.

Triamcinolone acetonide treatment

After the baseline objective and subjective assessments, another clinician gave an intralesional injection of 0.5 ml lidocaine 2% with 0.5 ml TA (40 mg/ml, Lisapharma S.p.A, Erba, Italy) to the experimental lesion, which would be concealed from the dentist performing clinical assessments until the therapeutic effect was analysed. The injection was placed directly into the subepithelial connective tissue just underline the ulceration base from adjacent normal mucosa. Moreover, patients were reassessed subjectively and objectively under instruction of the same clinician as the first visit. Follow up was carried out at 1-week interval. Over 2 weeks, if the treated ulceration regressed $<81\%$ in size, it would receive one more injection and was reassessed after 2 weeks. All controlled ulcerations were given therapeutic measurements from the third visit as it seemed inappropriate to deprive them from accession to appropriate therapy for more than 2 weeks.

Treatment response

The response of lesion to TA injection was evaluated on the basis of resolution in erythematous and ulcerative areas. It was classified as no response (NR; $<20\%$ reduction), partial response (PR; 20–49% reduction), good response (GR; 50–80% reduction), almost complete or complete response (CR; 81–100% reduction) and worsening.

Statistical analysis

The differences of VAS, lesion area and REU scores between experimental and control group were analysed by paired *t*-test. The ANOVA was used to test differences between measurements made at different times.

Probability value of < 0.05 (two-sided) was accepted as statistically significant for all statistical tests carried out in the present study by using SPSS® version 10.0 software (SPSS Inc., Chicago, IL, USA).

Results

Relief of symptoms and signs after intralesional TA injection

A total of 45 patients were enrolled in this study, providing 45 experimental sites and 45 control sites. The mean age was 50.5 ± 13.0 years ranging from 25 to 72 years, and 66.7% (30 of 45) of the participants were women.

During the 2-week study period, one TA injection significantly reduced painful symptoms, erythema and ulceration areas as recorded on Table 2. There was 55% reduction in VAS score for 1 week and 85% for 2 weeks in the experimental group, whereas the control group showed minimal change in VAS score ($P > 0.05$). Likewise, TA injection caused 55% and 57% reduction in erythema and ulceration areas for 1 week, respectively, as well as both 78% reductions after 2 weeks. All reductions of symptoms and signs were significant for the experimental group when comparing the mid-point measurements to baseline and the final measurements to mid-point measurements. However, in the control group the changes were not statistically significant.

At the end of 2 weeks, 23 (51.1%) patients gave more than 80% relief in ulceration size to one TA injection. Consequently, 22 (48.9%) patients were subjected to a second injection on experimental sites and followed up. Figure 1 showed their average lesion area and VAS score over the 4-week period respectively. Marked reductions were revealed on both subjective and objective measurements as indicated in Fig. 1 ($P < 0.05$).

Table 2 Comparison of VAS, erythematous and ulcerative areas, and REU score with or without intralesional TA injection within 2 weeks

	Baseline	*Mid-point (1 week)*	*Final (2 weeks)*
VAS (0–100)			
Experimental[a]	52.42 ± 11.72	23.98 ± 12.92	8.33 ± 10.11
Control[a]	51.36 ± 13.00	49.93 ± 13.19	49.69 ± 12.85
P-value[b]	0.68	< 0.001	< 0.001
Erythema (mm^2)			
Experimental[a]	155.78 ± 32.65	69.93 ± 28.98	32.82 ± 18.00
Control[a]	147.02 ± 28.65	145.22 ± 28.22	145.49 ± 29.05
P-value[b]	0.18	< 0.001	< 0.001
Ulceration (mm^2)			
Experimental[a]	34.27 ± 24.29	14.24 ± 11.64	7.64 ± 8.63
Control[a]	33.47 ± 21.95	32.73 ± 21.51	32.27 ± 19.90
P-value[b]	0.87	< 0.001	< 0.001
REU score			
Experimental[a]	6.01 ± 0.38	4.43 ± 0.66	3.83 ± 0.95
Control[a]	5.94 ± 0.49	5.94 ± 0.49	5.94 ± 0.49
P-value[b]	0.47	< 0.001	< 0.001

[a]Values are given as mean ± SD.
[b]Compared between experimental group and control group.
VAS, visual analogue scale; TA, triamcinolone acetonide.

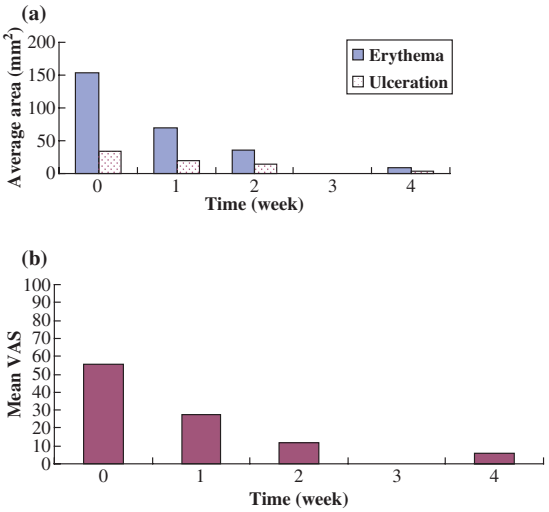

Figure 1 Mean surface areas of erythematous and ulcerative lesions (a), and mean visual analogue scale (VAS) score (b) over 4-week study period in 22 ulcerative oral lichen planus (OLP) patients who received two triamcinolone acetonide (TA) injections.

In addition, when clinical signs evaluated by the REU scoring system, similar statistical findings were noted between measurements made at different times in the experimental group, while the control group gave rise to no change (Table 2).

Treatment response to intralesional TA injection

Clinical response to TA injection in our study was displayed in Table 3. Of the 45 OLP patients after one TA injection, 32 (71.1%) patients gave CR in erythematous area, 23 (51.1%) in ulcerative area and 29 (64.4%) in total lesion area. Over the 4-week study period, total 40 (88.9%) patients showed CR in erythematous area and 38 (84.4%) in ulceration size, no matter receiving one or two injections. However, seven (15.6%) patients still gave < 81% resolution in ulceration size after two injections. Moreover, at the end of 4 weeks, a total of 39 (75.6%) patients gave CR in total lesion area and six (24.4%) patients giving GR.

Adverse effects of intralesional TA injection

No complications, such as pigmentation change, burning sensation or tingling sensation, were noted with the volume and concentration of TA injected in the present study.

Discussion

Our study indicated that intralesional TA injection was effective for signs and symptoms control of ulcerative OLP. A single TA injection resulted in rapid decrease in VAS score (52.42 vs. 8.33), erythematous area (155.78 mm vs. 32.82 mm), ulcerative area (34.27 mm vs. 7.64 mm) and REU score (6.01 vs. 3.83), which was sufficient in healing ulcer (CR) in 51.1% of patients, and reducing erythema in 71.1% of cases within 2 weeks. Over our 4-week study period, the average data for

Table 3 Treatment response of patients with ulcerative OLP to one to two TA injections by measurements of erythema and/or ulceration areas over 4-week study period

	Erythema		*Ulceration*		*Erythema + ulceration*	
Treatment response	$n = 23$[a]	$n = 22$[b]	$n = 23$[a]	$n = 22$[b]	$n = 23$[a]	$n = 22$[b]
1 injection						
Complete (>80%)	22	10	23	0	22	7
Good (50–80%)	1	10	0	15	1	13
Partial (20–49%)	0	2	0	7	0	2
None (<20%)	0	0	0	0	0	0
Worsening	0	0	0	0	0	0
2 injections						
Complete (>80%)		18		15		17
Good (50–80%)		4		5		5
Partial (20–49%)		0		2		0
None (<20%)		0		0		0
Worsening		0		0		0

[a]Patients received one TA injection.
[b]Patients received two TA injections totally at 2-week interval.
OLP, oral lichen planus; TA, triamcinolone acetonide.

lesion measurements and graphs depicting ulceration, erythema and pain illustrated trends in healing in the experimental group. At last, totally 88.9% and 84.4% of cases were observed complete resolution of erythema and ulceration respectively. Because OLP characteristically follows an unpredictable course of exacerbation and remission (2), a control group in the present study was important to evaluate the efficacy of TA injection vs. spontaneous remission. Thus, although the control group also achieved a lesser decrease in corresponding measurements that was not statistically significant.

The aetiology of OLP is unknown, but it has been proposed that OLP is caused by a cell-mediated immune response with an inflammatory infiltrating cell population composed of T lymphocytes (22–24). The efficacy of TA treatment in OLP is mainly attributed to the local anti-inflammatory effect and the anti-immunological properties of suppressing T-cell function (12, 24, 25). Triamcinolone is a fluorinated prednisolone derivative, and the 9-α fluoridation results in enhanced anti-inflammatory properties (12, 25). Thus, compared with the parent compound, TA aqueous injectable suspension is insoluble and remains longer at the injection site (12, 25). It has been reported that TA mouthwash or orabase gave satisfactory treatment outcomes in OLP patients (26, 27). By virtue of higher drug concentrations locally, TA injection seems giving an even faster response. Moreover, the treatment interval is better not <2 weeks in order to obtain better efficacy and avoid potential adverse reaction.

No adverse effects were reported due to intralesional TA injection in our study, although some complications of topical steroid therapy have been described by other investigators, such as candidiasis (27, 28), pigmentation (29, 30) and irritation (7). In general, our patients were satisfied with TA injection, and in most cases, they preferred TA injection on advantage of the simplicity and efficacy of this treatment procedure. Thus, it seems that TA injection is appropriate in treatment of other oral disease especially with localized, large or recalcitrant ulceration, such as chronic discoid lupus erythematosus (CDLE) on lips, oral traumatic ulceration and major aphthous ulcer. Notably, when microbial, fungal or virus infection is present, TA injection is not recommended.

Unfortunately, seven patients (15.6%) still gave no CR to TA injection. Patients who did not respond to two TA injections were more likely to experience non-resolution with further injections. Thus, these patients would be more likely to benefit from combining with other treatment measurements, such as other local or systemic corticosteroids (2, 4).

Recently, most study monitored OLP activity and treatment response according to lesion area changes (8, 9). Reticular lesion was always asymptomatic and persisted after intralesional TA injection in a short time as we observed earlier. In addition, erythema and ulceration were always symptomatic and were target lesions for treatment in our study. Thus, we did not measure surface area of reticular lesion. Swift et al. (1) tried another system to evaluate the efficacy of topical 1% pimecrolimus cream, in which the lesion area was measured and weighted by a factor according to severity. If lesion areas were ranked according to their size and substituted by the ranks, this simplified semiquantitative system would be similar with the REU scoring system described by Piboonniyom et al. (3). By the REU system, the reticular lesion was constantly scored 1 and remained unchanged after therapy in our study, so we used the REU system without modification and it gave good consistency with measurements of erythematous and ulcerative areas on assessing treatment outcomes.

In conclusion, intralesional TA injection is effective and safe in achieving lesion and pain resolution in ulcerative OLP. Most of the patients respond to one to two injections. If they fail to respond to two injections, other combining treatment modalities are reasonable. The REU scoring system is simple and effective in assessing short-term management outcomes of OLP. TA injection in other ulcerative oral diseases is suggested and needs further confirmation.

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