Review

Steriods in the treatment of lichen planus: a review

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Abstract: Steriods have been found to be effective in treating symptomatic oral lichen planus (OLP) by reducing pain and inflammation. In fact, systemic corticosteroids should be reserved for acute exacerbation, and multiple or widespread lesions. They may be indicated in patients whose condition is unresponsive to topical steroids. However, various potent topical steroids have been reported to be effective in the treatment of symptomatic OLP. They can be used as the first line drugs in the treatment of OLP with no serious side-effects. During the therapy, candidiasis was commonly found and in addition, bad taste, nausea, dry mouth, sore throat and swollen mouth may occur as minor side-effects from some topical steroids. Because OLP is a chronic disorder that requires long-term treatment, topical steroids are recommended for the treatment OLP because of minimal side-effects and the cost benefit. This manuscript reviews the use of steroids, especially its topical application, in the treatment of OLP. (J. Oral Sci. 50, 377-385, 2008)

Keywords: oral lichen planus; steroids; topical; side-effects.

Introduction

Oral lichen planus (OLP) is a chronic inflammatory condition that is probably of multifactorial origin, often idiopathic with an immunopathogenesis involving T-cells (1). Oral lesions that are caused by contact with dental materials are called oral lichenoid contact lesions (OLCL) while those which are induced by drugs are designated as oral lichenoid drug reactions (OLDR). Oral lichenoid lesions are almost indistinguishable from OLP, both clinically and histologically. The distinguishing feature of OLCL is that it shows direct topographic relationship to the suspected causative agent, most commonly amalgam. The removal and replacement of the putative causative materials result in the resolution of OLCL within several months. On the other hand, oral lichenoid drug reactions (OLDR) arise in association with the taking of certain medications, e.g., oral hypoglycemic agents, angiotensin-converting enzyme inhibitors, and nonsteroidal anti-inflammatory agents (2,3). Both OLP and oral lichenoid lesions share similar histopathologic features (Fig. 1). Oral lichen planus is often characterized by a bandlike lymphocytic infiltrate in the lamina propria and liquefactive degeneration of basal keratinocytes (1).

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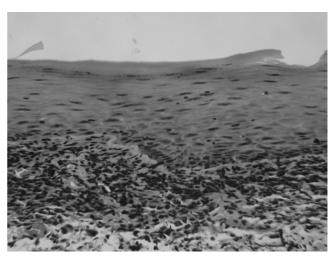Fax: +66-2-2188818
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Fig.1 Photomicrograph showing keratinized stratified squamous epithelium with areas of basal cell degeneration covering the connective tissue and band of lymphocytes underneath the epithelial layer. (H-E staining, original magnification ×40)

The etiopathogenesis of OLP has now been better clarified based on the mechanisms involved and appears to be complex, with interactions related to genetic, environmental, and lifestyle factors (4). Many factors are involved in the pathogenesis of OLP such as matrix metalloproteinases, chymase, tryptase and proinflammatory cytokines (5). Recently, TNF-α which is one of the proinflammatory cytokines has been reported to play a role in the pathogenesis and inflammatory process of OLP (6). The immunological abnormality leads to a delay in the growth of mucosal epithelium which is responsible for hyperkeratosis (7). OLP is a relatively common inflammatory mucocutaneous disease affecting middle-aged patients comprising between 0.5 and 2.2% of the population in epidemiological studies (3,8). The oral lesions are often asymptomatic but the atrophic-erosive form of OLP can cause symptoms ranging from burning sensation to severe pain, resulting in difficulty in speaking, eating and swallowing (9-11). Patients with symptomatic OLP often require therapy to reduce signs and symptoms of the condition (12) and they should be treated, if symptoms are significant (13).

Symptomatic OLP was mainly encountered in those with the erosive form and about 90.9% of the patients had multiple oral sites of involvement. The erosive presentations showed significantly longer duration, more sites are affected (oral, genital, oesophageal) and greater prevalence in old patients than the reticular or atrophic ones (14).

The management of OLP varies considerably between patients, and for individual patients, due to fluctuations in the disease activity (8,15). Because of its chronic nature, the patients' medical history, psychological state, treatment compliance as well as possible drug interaction should be considered when evaluating the cost effectiveness of any treatment modalities in the management of OLP (16). Moreover, the medication should be discontinued when the onset of the lesion is related to the use of drugs (17).

Therapeutic Effects of Steroids in OLP

Various treatment regimens have been attempted to improve the refractory lesions, but a complete cure of OLP has not yet been accomplished because of its recalcitrant nature (16,18). However, adverse effects are common even with short courses of steroids such as insomnia, mood swings, fatigue, fluid retention, and others (13). In fact, systemic corticosteroids should be reserved for acute exacerbation, and multiple or widespread lesions (3,19). Moreover, they may be indicated in patients whose condition is unresponsive to topical steroids (20).

The dosage of systemic steroid must be tailored for individual patients depending on the severity of the lesion, the patient's weight and the patient's response to treatment. For example, with a short course of corticosteroids such as prednisolone, the drug should be administered at 0.5 to 1.0 mg/kg of the patient's body weight per day. When the therapeutic response has been achieved, the dosage of steroid can be rapidly tapered to minimize the significant adverse effects (3).

Topical corticosteroids are widely used in the treatment of vesiculo-erosive diseases of the oral mucosa including OLP to reduce pain and inflammation (21). Many trials and formulations of steroids have been used in the treatment of OLP. Interestingly, in the Cochrane review of placebo-controlled randomized clinical trials of treatments used for symptomatic OLP, 11 interventions were grouped into four therapeutic classes (topical cyclosporins, topical or systemic retinoids, topical steroids and phototherapy) for comparison. The main outcome measures noted were improvement of signs (erythema, reticulation, ulceration) and symptoms (pain, discomfort) usually after 8 weeks of therapy. Only systemic agents were associated with treatment toxicities whereas all other side-effects were mild and mainly local. The results were tempered by the small sample size, lack of replication, lack of standardized outcome measures and the very high likelihood of publication bias. Therefore, this review only provided evidence for the superiority of the assessed interventions over placebo for the palliation of symptomatic OLP (22).

However, some topical steroids have been shown to be beneficial to some extent when applied onto the lesions. Topical fluocinonide 0.05% in an adhesive base improved OLP lesions with no adverse effects (23). In a randomized, double-blind, placebo-controlled study, the efficacy of the topical application of 0.025% fluocinonide was evaluated in forty patients with OLP. All patients were followed for 3 to 17 months. No adverse effect was noted during the follow-up period. In the group of 20 patients who received the drug, 4 patients (20%) showed complete remission, and 12 patients (60%) had a good or partial response to topical treatment whereas in the placebo-group, there was absolutely no complete remission and only 6 (30%) showed partial remission. In the placebo-group (70%) did not respond at all to the treatment. These results suggest that topical application of fluocinonide in an adhesive base is safe and effective in reducing signs and symptoms in OLP (24).

Topical steroids such as betamethasone showed effectiveness in the treatment of symptomatic OLP in another study (17). Hydrocortisone hemisuccinate in aqueous solution is often of little benefit in treating OLP (25). Fluticasone propionate spray and betamethasone sodium phosphate mouthrinse have been used effectively

in the short-term management of symptomatic OLP (26). Topical steroids such as mometasone furoate microemulsion caused a statistically significant reduction in pain in erosive-ulcerative OLP. This treatment significantly reduced the surface area of erythema and ulceration. None of these patients suffered severe adverse effects. Thus, mometasone furoate microemulsion may be safe and effective for the treatment of symptomatic erosive-ulcerative OLP (27).

Clobetasol propionate in various forms such as orabase, ointment or aqueous solution has also been shown to be effective for OLP in many studies (28-31). Moreover, 65% of OLP patients treated with topical clobetasol showed disease-free periods after 6 months of follow-up (29). In combined treatment of systemic and topical steroids, atrophic-erosive OLP was treated systemically with prednisone (50 mg/day), and subsequently with clobetasol ointment in an adhesive medium plus antimycotics; whereas the control group was only treated topically with clobetasol plus antimycotics. Complete remission of signs and symptoms were similar. Follow-up showed no significant differences between the two groups. Therefore, the most suitable corticosteroid therapy in the management of OLP is the topical therapy, which is easier and more cost-effective than the systemic therapy followed by topical treatment (32). The application of clobetasol 17-propionate orabase paste 0.05% plus 100,000 IU/ml of nystatin by means of a tray appeared to be an efficacious treatment for severe erosive gingival lesions and showed complete response in all 33 cases over the 48-week period (33).

Clobetasol-17-propionate in the form of topical application has been reported as an efficacious therapy in atrophic-erosive OLP, without exposing the patient to systemic side-effects. Fifty patients with symptomatic OLP were enrolled in a controlled single-blind phase IV clinical trial. These results suggest that the new topical drug delivery system may enhance, at least in terms of symptom remission and compliance, the effectiveness of clobetasol propionate at a dose of 0.025% in OLP therapy (34). Furthermore, a recent study has shown that clobetasol is more effective than cyclosporine in inducing clinical improvement in atrophic-erosive OLP (35). This study was a double-blind randomized controlled trial in the treatment of symptomatic OLP that reported clinical assessments, adverse effects, cost-effectiveness and complete follow-up.

The effects of topical clobetasol propionate with and without a topical antifungal drug (miconazole) were compared based on the symptoms of thirty-five OLP patients. A randomized, parallel, double-blind trial was conducted in patients with OLP. They were randomly assigned to receive either clobetasol propionate and miconazole, or clobetasol propionate and placebo for 6 weeks. All the patients showed clinical and subjective improvements within 3 weeks. However, the addition of miconazole did not significantly improve the signs and symptoms of OLP. Moreover, no case of clinical candidosis was seen in the patients taking miconazole, while one-third (5 of 15) of the placebo group were affected. Although miconazole can prevent iatrogenic candidosis, the addition of this antifungal drug to clobetasol propionate treatment does not improve the efficacy of the therapy (36). It has been reported that clobetasol 0.05% was found to be as useful as tacrolimus 0.1% in the treatment of OLP in another study (37).

Triamcinolone acetonide in the forms of mouthwash and orabase were compared in the treatment of 20 cases of OLP (38). The patients were instructed to use medication four times daily-after meals and before bed time. The results showed that triamcinolone acetonide mouthwash had a satisfactory shelf life and was well accepted by the OLP patients. Moreover, there was no significant difference in therapeutic efficacy from the commercial paste dosage form in the treatment of OLP in that study. The intralesional triamcinolone acetonide (TA) 0.5 ml (40 mg/ml) injection was employed for the treatment of symptomatic OLP. TA was injected on one side of the buccal mucosa of ulcerative OLP while the other side served as a control in patients with bilateral buccal mucosal lesions. TA injections were shown to be effective and safe in reducing signs and symptoms of OLP. No complication was noted with such TA injections (39).

Interestingly, a large randomized controlled trial which compared steroid with cyclosporine for the topical treatment of Asian patients with OLP indicated that triamcinolone acetonide 0.1% in orabase (TAO) showed better results than cyclosporine (40). Furthermore, another study also showed that topical cyclosporine did not provide any beneficial effect and was not more effective than TAO 0.1% in the treatment of Thai patients with symptomatic OLP (41). Recently, triamcinolone acetonide mouthrinse at the concentration of 0.3% or 0.5% was shown to be appropriate for the treatment of erosive OLP and only 4 out of 35 cases (11.4%) developed candidiasis. In that study, the risk of fungal superinfection was low (42).

The efficacy of topical tacrolimus ointment has been compared with that of triamcinolone acetonide ointment in patients with OLP. Twenty patients in each group were treated with topical tacrolimus 0.1% ointment or triamcinolone acetonide 0.1% ointment 4 times daily. The clinical effect was graded after 6 weeks. The most common side-effects in both groups were temporary burning or stinging at the site of application. Topical tacrolimus 0.1%
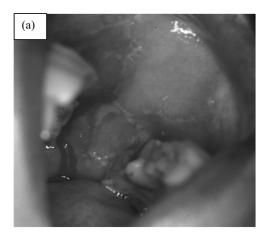
ointment showed a better initial therapeutic response than triamcinolone acetonide 0.1% ointment. However, relapses occurred frequently within 3-9 weeks of the cessation of the treatment (43).
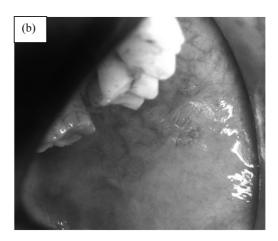
In a blinded parallel-group randomized clinical trial, the efficacy and safety of pimecrolimus 1% cream and triamcinolone acetonide 0.1% paste were evaluated in treating 40 patients with OLP four times daily for a total of 2 months with follow-up for another 2 months. The results showed that both pimecrolimus and triamcinolone groups showed significant improvement in all measured efficacy end points throughout the visits. Two patients in the pimecrolimus group experienced prominent, but transient burning sensation, whereas none of the patients in the triamcinolone group had any prominent adverse events. This study showed that patients with OLP may benefit from both topical pimecrolimus and triamcinolone acetonide therapy with minimal side effects (44).

Recently, one randomized comparative study showed that betamethasone oral mini-pulse therapy improved the clinical outcome in patients with moderate to severe OLP and it was equally effective when compared with topical triamcinolone acetonide 0.1% paste but the response was earlier, especially in treating erosive disease (45).

When compared with TAO 0.1%, fluocinolone acetonide 0.1% in orabase (FAO) has been shown to be more effective than TAO in the treatment of OLP (46). Moreover, various forms of topical steroid applications such as fluocinolone acetonide 0.1% in solution (FAS), FAO in conjunction with solution (FAO/FAS) has been reported in patients with OLP in a 2-year treatment and the results showed complete remission in 77.3% of the patients treated with FAO (15). The researchers concluded that FAO can produce improved results in the management of OLP by long-term follow-up (Fig. 2). Moreover, FAS 0.1% can be used effectively in the treatment of recalcitrant and longstanding lip LP (Fig. 3). Furthermore, compared with retinoic acid gel 0.05%, FAO 0.1% has been shown to be more effective
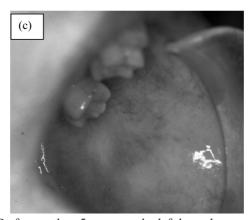

Fig. 2 (a) Recalcitrant OLP of more than 5 years on the left buccal mucosa with white striae and bleeding before treatment in a 55-year-old woman, (b) Two weeks after treatment with fluocinolone acetonide 0.1% in orabase, the OLP lesion showed marked improvement, (c) After 3 years during follow-up treatment with fluocinolone acetonide 0.1% in orabase, the left buccal mucosa showed complete remission.

(47). Moreover, the comparison between the efficacy of fluocinolone acetonide gel 0.1% with FAO 0.1% in 48 patients with OLP revealed no statistically significant differences in clinical score changes and FAO 0.1% provided similar efficacy in the treatment of OLP (48).

Recently, FAO 0.1% has been shown to have a beneficial effect on the reduction of TNF-α expression by inhibiting the synthesis of this cytokine. TNF-α is involved in the inflammatory process of OLP in Thai patients. This finding was the first report regarding the potential of a topical steroid in affecting the expression of TNF-α in OLP lesions (6).

In the study of saliva in 13 OLP subjects who were treated with 0.1% dexamethasone oral rinse for 6 weeks, the levels of cytokines such as TNF-alpha, IL-1-alpha, IL-6, and IL-8 were decreased significantly. These preliminary results indicate that dexamethasone can reduce some cytokines involved in the pathogenesis of OLP. Moreover, salivary analysis of NF-κB-dependent cytokines may be applied to monitor the therapeutic response of OLP (49).

From these points of view, topical steroid is recommended as the first line of therapy for patients with symptomatic OLP (Table 1) because of minimal side-effects and cost benefit in long-term treatment. It can be used alone or in combination with systemic steroid.

Side-effects of Steroids

It is an interesting fact that systemic absorption and adrenal suppression from superpotent topical steroids in the treatment of chronic skin diseases were reported (50,51). However, adrenal suppression is not found in long-term application of topical corticosteroids used for the management of OLP such as fluocinonide 0.05%; fluocinolone acetonide 0.1% and clobetasol 0.05% (29,46,52), but treatment of OLP with clobetasol propionate 0.05% mouthwash can cause mild adverse effects (moon face and hirsutism) between week 4 and week 6 of treatment (31). Other minor adverse effects have been associated with fluticasone propionate spray such as bad taste and smell, nausea, dry mouth, sore throat, swollen mouth and candidiasis (26). Fungal overgrowth of normal oral flora by *Candida* leading to candidiasis was the only common side-effect arising from topical corticosteroid therapy
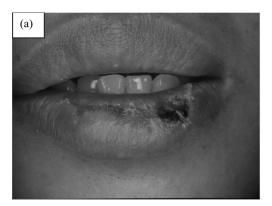

Fig. 3 (a) Longstanding isolated LP of the lower lip of more than 3 years with haemorrhagic crust in a 27-year-old woman, (b) Two weeks after treatment with fluocinolone acetonide 0.1% in solution, the haemorrhagic crust showed reduction in size, (c) One year after treatment with fluocinolone acetonide 0.1% in solution, LP lesion on the lip showed significant improvement.

Table 1   Report of topical steroids in the treatment of OLP [Modified from Carrozzo and Gandolfo 1999 (9); Lodi et al. 2005 (18)]

Drug	Reference	Patients (n)	Results (%)			Duration (weeks)	Study type
			CR	PR	NR		
Betamethasone sodium phosphate	McGrath et al. 2003 (17)	44	UK	50	UK	6	Single-blind
	Hegarty et al. 2002 (26)	44	-	73	27	6	Comparative
Clobetasol propionate	Sardella et al. 1998 (28)	14	57	22.5	22.5	4	Comparative
	Carbone et al. 1999 (29)	20	75	25	-	24	Placebo-controlled, Comparative
	Lo Muzio et al. 2001 (30)	24	100	-	-	2	Comparative
	Gonzalez-Moles et al. 2002 (31)	30	93	-	7	48	Open
	Carbone et al. 2003 (32)	23	69.6	26	4.4	24	Comparative
	Campisi et al. 2004 (34)	17	70.6	11.8	17.6	8	Controlled, single-blind
	Conrotto et al. 2006 (35)	19	47.4	47.4	5.2	8	Randomized, double-blind, Comparative
Fluocinonide	Voûte et al. 1993 (24)	20	20	60	20	9	Placebo-controlled
	Carbone et al. 1999 (29)	20	25	65	10	24	Placebo-controlled, Comparative
Fluocinolone acetonide	Thongprasom et al. 1992 (46)	19	68	UK	UK	4	Comparative
Fluticasone propionate	Hegarty et al. 2002 (26)	44	-	80	20	6	Comparative
Hydrocortisone hemisuccinate	Holbrook 1998 (25)	54	48	37	15	2-4	Open
Triamcinolone acetonide	Thongprasom et al. 1992 (46)	19	42	UK	UK	4	Comparative
	Malhotra et al. 2008 (45)	24	→	66§	UK	24	Randomized, Comparative

CR = complete remission, PR = partial remission, NR = No response, UK = unknown
§ reported as good to excellent response

(15,46). However, candidiasis can be controlled or prevented by using anti-fungal therapy (eg, miconazole gel alone or in combination with nystatin suspension) in topical corticosteroids (15,29,31,46). Even though the intralesional injection of corticosteroids can induce the healing of the longstanding lesions and improve the symptoms, it can have a localized side-effect such as mucosal atrophy (1,53).

However, the side-effects can be due to the absorption of topical steroid from oral mucosa mainly by direct absorption or by ingestion following incorrect use of the preparations. In addition, the precise risk factors for the side-effects of topical steroids such as age of the patient, treatment modalities, concomitant medications, time of application, site or size of the lesions, and ulcerated area of the lesions have not been studied; therefore, future research on these risk factors should be carried out to provide more information. At present, topical cortico-steroids seem to be safe when applied to oral mucous membranes and they were effective in the treatment of OLP with no serious side-effects in many studies.

Recommendations

- A potent topical corticosteroid is the first-line of treatment for symptomatic oral lichen planus at any site.
- Asymptomatic oral lichen planus need not to be treated, but follow-up is recommended.
- Removal of irritation from sharp cusps, broken restorations and non-opposing tooth is recommended. Control of oral hygiene is found to be of benefit in the management of OLP.
- If *Candida* superimposes on the lesions of OLP before or during therapy, it should be treated with antifungal drugs.
- Long-term follow-up should be reserved for patients with complicated OLP and those unresponsive to treatment.
- Tissue areas that do not respond to treatment may need further evaluation and possibly future biopsy.
- Biopsy is indicated if malignancy change is suspected.

In summary, potent topical steroids are recommended as the first drug of choice in the treatment of symptomatic OLP. Clobetasol, fluocinolone acetonide, fluocinonide or others potent topical steroids have been found to be reliable and effective drugs in the treatment of OLP. Topical treatment can be used with systemic corticosteroids in the treatment of OLP to reduce the systemic side-effects or it can be used alone. Various forms of topical steroids such as orabase, ointment, solution, spray or mouthwash have been used in the treatment of OLP. However, the management of OLP patients on which topical vehicles, systemic steroids or the combination of both is dependent on professional judgement. Moreover, different formu-lations, dosages, and potencies of topical steroids have shown different effects in the treatment of OLP in many

studies. These differences of various topical steroids affect the treatment response. In conclusion, there can not be a uniform approach to the treatment and management of OLP because it varies from individual to individual. Control of oral hygiene is the most important consideration during management of OLP and can enhance healing of the lesions (15,54). Appropriate management of OLP will help to control pain and significantly improve the quality of life for many patients (55).

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