Clinical evaluation in treatment of oral lichen planus with topical fluocinolone acetonide: a 2-year follow-up

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Abstract

Background: Oral lichen planus (OLP) is a chronic inflammatory disease which is recalcitrant to medical treatment. The purpose of this study was to compare the effectiveness of various forms of the topical steroid fluocinolone acetonide applications in patients with OLP.

Methods: Data of OLP patients were collected retrospectively from the chart record and the 97 OLP patients were divided into three groups. The first group ($n = 28$) was treated with a 0.1% solution of fluocinolone acetonide (FAS), the second group ($n = 22$) with 0.1% fluocinolone acetonide in orabase (FAO), and the third group ($n = 47$) with both FAS and FAO (FAS/FAO) throughout the study. Each group was clinically evaluated as complete remission (CR), partial remission (PR), or no response (NR), following the treatment. Also, the side-effect of oral candidiasis was recorded in each group.

Results: Two years of treatment resulted in complete remission of 77.3, 21.4, and 17.0% of patients in the FAO, FAS, and FAS/FAO groups, respectively. There was a statistically significant difference in disease remission ($P < 0.05$), but not in oral candidiasis appearance ($P > 0.05$) among various forms of topical steroid application.

Conclusion: The study concluded that FAO or FAS can produce improved results in the management of OLP by long-term follow-up.

Keywords: candidiasis; fluocinolone acetonide; oral lichen planus


Oral lichen planus (OLP) is a relatively common inflammatory disease, probably of multifactorial origin and sometimes induced by drugs or dental materials, often idiopathic, and with an immunopathogenesis involving T-cells (1). A recent study reported the hypothesis that this disease is a delayed-type hypersensitivity or cell-mediated response to an antigen stimulus residing within the epithelium (2). New associations such as those with hepatitis C virus infection have emerged (3–5). Interestingly, a recent study has reported a case of chronic active viral C hepatitis presented with erosive OLP during a course of interferon alpha-2a therapy (6). However, the etiology of OLP is still controversial. Various treatment regimens have been
attempted to improve the refractory lesions, especially in atrophic-erosive OLP, but a complete cure has not been accomplished because of its recalcitrant nature (7, 8). Therefore, steroids have been widely used for reducing pain and inflammation. Potent topical steroid applications such as 0.05% fluocinonide and 0.05% clobetasone propionate have been used with beneficial effects regarding control of symptoms and signs of OLP with minimal side-effects (9). Moreover, there was no adrenal suppression in OLP patients treated with 0.1% fluocinolone acetonide in orabase (FAO) in one study (10). Systemic retinoids have been successful in treatment of OLP but there are some side-effects including dryness of skin and mucosa, skin rashes and itching, and elevations in the serum γ-GT, SGOT, and SGPT (11–14). A topical retinoid has also been suggested for the treatment of OLP due to its immunomodulating effect (15). The comparison between 0.1% FAO and topical retinoic acid in orabase showed that FAO could reduce the severity of atrophic-erosive OLP better than 0.05% retinoic acid ($P = 0.01$; 16). A low dose of cyclosporin rinse has also been used in the treatment of OLP and proved to be an effective therapy (17, 18). This drug is very expensive and has yielded a slight clinical improvement when treating severe OLP in some studies (19–22). Recently, some reports of topical tacrolimus treatment in OLP were shown and the treatment appeared to be an effective therapy to control symptoms and clear lesions of symptomatic OLP (23–26). Nevertheless, tacrolimus is an immunosuppressant and strong medicine; the first reported case of severe recalcitrant major recurrent oral ulcers was associated with the administration of systemic tacrolimus in a liver transplantation recipient (27). Thus, it may not be a good medication generally available for use in all cases of symptomatic OLP. There are no treatment regimens to cure this disease because of its chronic nature. However, some studies reported that the spontaneous remission of OLP itself occurred between 6.5 and 23% of cases by the time of the latest consultation (28, 29). Therefore, a potent topical steroid may be suitable for symptomatic treatment of OLP, especially in its atrophic-erosive form. The purpose of this study was to compare the effectiveness of various forms of 0.1% fluocinolone acetonide applications and subsequent oral candidiasis in patients with OLP in long-term follow-up.

Patients and methods

Data of 97 OLP patients at the Oral Medicine Department, Faculty of Dentistry, Chulalongkorn University was collected retrospectively from the hospital charts during 1984–98. All patients had been diagnosed clinically with OLP and confirmed by histopathological findings. Oral examination of the lesions was performed by one clinician only (first author). Gender, age, medical history, symptoms, types, and sites of the lesions and duration of disease were recorded. The OLP lesions were scored according to the criteria scale described and modified by Thongprasom et al. (10):

- Score 5: white striae with erosive area >1 cm².
- Score 4: white striae with erosive area <1 cm².
- Score 3: white striae with erythematous area >1 cm².
- Score 2: white striae with erythematous area <1 cm².
- Score 1: mild white striae only.
- Score 0: no lesions, normal mucosa.

All the patients with OLP had symptoms such as roughness, burning sensation, and pain and required treatment. Consent was obtained from the patients before starting treatment. The patients were randomly selected from each of the three treatment groups. The first group ($n = 28$) had been treated with 0.1% fluocinolone acetonide in solution (FAS) only and the second group ($n = 22$) with 0.1% FAO only throughout the study. Patients who responded to the drug they had been started on, i.e. FAS or FAO, continued treatment with the same drug. The patients who responded slightly to FAS or FAO over a duration of approximately 6 months were switched over to FAS or FAO instead and were subsequently studied as the third group (FAS/FAO) ($n = 47$).

The patients were asked to stop medications for the OLP lesions for at least 2 weeks before starting treatment. They were advised to apply FAS or FAO topically to the lesions three times a day for 1 month. When the lesions responded to the treatment, the patients were instructed to apply FAS or FAO twice a day and then gradually reduce it to once a day until complete remission had been achieved. The patients in each group were recalled to the Oral Medicine Clinic for evaluating the effectiveness of the treatment. Evaluations by oral examinations together with photographs were performed at 2 weeks, 1 month, 6 months, 1 year, 1.5 years, and 2 years, respectively. After completion of treatment, the lesions were assessed according to the following criteria:

- Complete remission (CR): no symptoms or very mild symptoms, lesions disappear or mild white striae (Fig. 1a,b).
- Partial remission (PR): symptoms reduced, mild white striae and mild erythematous area (Fig. 2a,b).
- No response (NR): symptoms persisted with no improvement or worsening of the lesions (Fig. 3a,b).

Oral candidiasis was diagnosed by clinical findings of a white plaque, which could be scraped off, and red patches, both of which underwent 10% KOH and periodic acid Schiff staining. The side-effect of candidiasis after treatment in all treatment groups
Fig. 1. Complete remission of OLP lesion (a) before and (b) after treatment.

Fig. 2. Partial remission of OLP lesion (a) before and (b) after treatment.

Fig. 3. No response of OLP lesion (a) before and (b) after treatment.
had been recorded during the follow-up period of 2 weeks, 1 month, 6 months, 1 year, and every 6 months thereafter. The data were analyzed by chi-square test.

Results

The OLP patients were predominantly women (75 of 97), and the mean age was 45.53 ± 13.16, ranging from 21 to 80 years. There were no statistically significant gender differences in the three groups \( (P = 0.499) \). The age of OLP patients also showed that there was no significant difference among the three treatment groups \( (P = 0.511) \).

Some patients had histories of atopy or drug allergies (36.08%), hypertension (15.46%), diabetes mellitus (9.28%), and other systemic diseases such as heart diseases, rheumatoid arthritis, blood diseases, hepatitis, etc. (21.6%) (Table 1). Anti-hypertensive drugs which the OLP patients were taking were commonly found, for example metyldopa, atenolol, and reserpine, respectively. The drug histories of the patients with diabetes mellitus included glibenclamide, metformin, and insulin injection.

Oral lichen planus patients complained of a burning sensation (70.10%) and pain (37.11%), while others complained of roughness (11.34%) (Table 2). Although the burning sensation was more frequent in OLP patients, the occurrence of all symptoms was not significantly different among the three groups \( (P = 0.325) \). The types of OLP lesions observed were most commonly atrophic–erosive (89.69%) and reticular (10.31%). The types of OLP lesions were not significantly different among the three groups \( (P > 0.05) \).

The sites of OLP lesions were most commonly found at the buccal mucosa (83.50%), gingiva (25.77%), mucobuccal fold (14.43%), labial mucosa (17.5%), tongue (13.4%), palate (13.4%), and floor of the mouth (3.0%) (Fig. 4). Most of the patients had more than one site of lesions. Although there was a statistically significant difference in the frequency of no buccal mucosa sites between the three treatment groups \( (P = 0.044) \), the buccal mucosa area, which was the most common site of the lesions in each group, showed no statistically significant differences \( (P = 0.883) \). Furthermore, a minority of OLP patients in this study had skin lesions (6.18%). The duration of disease before onset of treatment was between 0.5 and 120 months, with a mean of 11.42 ± 18.65 months.

During the course of follow-up, the first 2 years of treatment resulted in complete remissions in 77.3, 21.4, and 17.0% of patients in the FAO, FAS, and FAS/FAO groups, respectively (Fig. 5). There was a statistically significant difference of disease remission \( (P < 0.05) \) among various forms of topical steroid application. Moreover, one case who had been treated with topical fluocinolone acetonide showed a complete remission after the 8-month treatment, and she had no symptoms with very mild white striae (score 0–1) throughout 10-year follow-up (Fig. 6a,b). Another case with severe OLP at the first visit showed normal gingiva after 4-year treatment with fluocinolone acetonide (Fig. 7a,b) and no recurrence during the latest follow-up for 10 years.

Table 2. Symptoms and types of OLP patients in three groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Symptoms (%)</th>
<th>Type of OLP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Burning</td>
<td>Pain</td>
</tr>
<tr>
<td>FAS</td>
<td>28</td>
<td>18 (64.3)</td>
</tr>
<tr>
<td>FAO</td>
<td>22</td>
<td>18 (81.8)</td>
</tr>
<tr>
<td>FAS/FAO</td>
<td>47</td>
<td>32 (68.1)</td>
</tr>
<tr>
<td>Total</td>
<td>97</td>
<td>68 (70.10)</td>
</tr>
</tbody>
</table>

*Roughness.

Fig. 4. The sites of OLP lesions in three groups.

Table 1. Gender, age, and medical history of patients with OLP in three groups

<table>
<thead>
<tr>
<th>Gender (%)</th>
<th>Systemic diseases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>No.</td>
</tr>
<tr>
<td>------------</td>
<td>-----</td>
</tr>
<tr>
<td>FAS</td>
<td>28</td>
</tr>
<tr>
<td>FAO</td>
<td>22</td>
</tr>
<tr>
<td>FAS/FAO</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>97</td>
</tr>
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</table>
The percentage of OLP patients with oral candidiasis in the three groups after treatment was 38.3, 14.3, and 13.6% in the FAS/FAO, FAS, and FAO groups, respectively. Oral candidiasis superimposed on the lesions of OLP was found in only three cases (3.09%) at the first presentation before initiating therapy. Candidiasis appeared between 1 and 24 months after the start of therapy. Acute pseudomembranous candidiasis was most commonly found in the areas of drug application. There was no statistically significant difference in the oral candidiasis appearance ($P > 0.05$) among the various forms of topical steroid application.

**Discussion**

In this study, OLP predominantly affected women (female/male ratio = 3:1) as noted in a previous study (30). This disease
commonly occurs in middle-aged patients (mean age = 45 years). Other medical conditions recorded in these OLP patients were: atopy, drug allergies such as to sulphonamides and penicillin followed by hypertension, diabetes mellitus, and other conditions, respectively. Liver disease and hepatitis C virus infection were found in only three cases, unlike the findings reported previously (31, 32). Only 6.18% of the OLP patients had skin lesions appearing along with the oral lesions. Patients often complained of a burning sensation and pain before the start of treatment. During 2 years of treatment with various forms of topical 0.1% flucinolone acetonide, the FAO group showed complete remission in 77.3% of the cases. A case in Fig. 6 neither had history of any systemic diseases nor had the regular taking of drugs. On her first visit, she had a severe atrophic-erosive area with pseudomembranous candidiasis on both sides of the buccal mucosa and gingiva. The lesions showed gradually resolved on the entire oral mucosa after treatment with fluconolone acetonide. She was a good example of a patient who cooperated with our treatment. She attended our clinic for every appointment, and healthy oral mucosa was seen by the time of the latest 10-year follow-up. The response of the OLP lesions varied with the penetration and absorption of the drugs into the oral mucosa. The delivery of drugs via the mucous membrane lining the oral cavity depended on the structure and composition of the mucosa (33, 34). Therefore, FAO or FAS may deliver drugs into the lesions to induce healing by different means and may vary in individuals. A role of immune response in OLP patients and the mechanism of fluconolone acetonide transported into the lesions suggest further investigation for clarification.

In susceptible OLP individuals, chronic presentation of antigen by basal keratinocytes may perpetuate the condition and direct cell-mediated immune damage on the keratinocytes (35). Extrinsic antigens in OLP may come from a number of sources, including food, bacterial flora, and dental materials. This suggests that OLP is unlikely to be caused by a single antigen. Some studies have not revealed the use of a restricted number of different T-cell receptor variable region genes (36, 37). The findings of known antigens are very important to eliminate the cause of chronic presentation in OLP. Treatment in chronic and refractory OLP would not be the exact rules regimes, but the management of such cases will vary in individuals.

Oral candidiasis occurrence in the FAS/FAO group was higher than that in the FAO group. It is recognized that oral candidiasis is a common side-effect of topical steroid application for treatment of oral lesions (38-41). Acute pseudomembranous candidiasis appearance was most commonly found in the area of drug application. The frequency of candidiasis eruption in the area of treatment of OLP lesions depended on prolonged use of FAS, FAO, or FAS/FAO. Some patients applied these drugs more frequently than prescribed. Excessive steroid application, especially in cases of patients with diabetes mellitus, could result in oral candidiasis. It is not necessary to discontinue the use of FAO or FAS in order to control acute pseudomembranous candidiasis. Moreover, it is essential to continue the anti-fungal medication during the use of the topical steroids in order to prevent recurrence. Several studies, both mycological and histological, have shown an increase in prevalence of candida infection studies in OLP (42, 43). Because of the high frequency of candida infection during corticosteroid therapy, anti-fungal drug such as miconazole gel may be effective for clinical improvement (10, 40, 44, 45). However, it appears to be easy to control with topical anti-fungal therapy. Miconazole gel resolved the oral candidiasis completely in every case in this study.

The findings from this study suggest that fluconolone acetonide (0.1%) can initially be used to manage OLP. Because of the chronic nature of this disease, it is difficult to cure OLP. Treating the symptoms is extremely important, and potent medications always involve a consideration of drug benefits weighed against potential adverse side-effects (46). Intranasal injections of triamcinolone (10 mg/cc) may be quite beneficial for slow-healing, atrophic-erosive OLP (47, 48). However, the injections can be extremely effective in inducing the healing of lesions, but they have a very localized effect such as mucosal atrophy (1, 49).

Although many studies have claimed the effectiveness of cyclosporin, the disadvantages of this medication are: bad taste and minor sensitivity of the mucosal surface on initial application in some patients (22, 50). Photochemotherapy with 8-methoxypsoralsens and PUVA has been found to be effective in the treatment of erosive OLP. This treatment may be useful for severe forms of erosive OLP that do not respond to conventional treatment (51, 52). On the other hand, classical PUVA therapy seems to have many side-effects such as nausea, dizziness, eye symptoms, paresthesia, and headache (53). Moreover, one matter for concern is that long-wave ultraviolet-A (PUVA) therapy has been shown to have oncogenic potential (54). Thus, topical application of psoralen is promising but still experimental.

In our study, successful management of OLP is heavily dependent upon the cooperation of the patient. The case in Fig. 7 is one good example of successful management of OLP. Oral hygiene control by periodontal and operative treatment during the administration of topical steroid fluconolone acetonide occurred with this patient at each appointment. Recommendations to this patient to avoid such precipitating factors as exposure to chemical substances from his job was found to be of benefit as far as the
treatment was concerned. Complete remission was revealed by normal and healthy gingiva after 4 years of treatment which was very different from the first visit. No recurrence of the lesion was found in this case after 10-year follow-up (July 2002).

In my opinion, it is unlikely that there is a single specific antigen responsible for OLP. Genetic background for immune-mediated diseases may cope with different harmful agents. Identification of susceptibility genes is important because susceptibility genes encode proteins that are most probably involved in the disease process (55). However, elimination of the microbial plaque comprising the supra- and subgingival biofilms in the oral cavity is also important and can enhance healing of OLP lesions. Because OLP is an incurable disease, reduction of the symptoms with topical steroid and controlled oral hygiene are necessary and important for maintenance of the quality of life in these patients.

Among the many treatments available, high-potency topical steroids remain the most reliably effective, though topical cyclosporine, topical tacrolimus, or systemic corticosteroids may be indicated in patients whose condition is unresponsive to topical steroids (56). Therefore, topical steroids such as FAS or FAO may be a useful, safe, and effective alternative therapy in the treatment of OLP. No serious adverse effects resulting from treatment with FAO or FAS occurred during long-term follow-up in our study.

References


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