RESEARCH ARTICLES

Topical Pimecrolimus 1% Cream in Treatment of Oral Lichen Planus

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Abstract

Oral lichen planus (OLP) is a common inflammatory disease of unknown etiology. The immunopathogenesis is T-cell mediated autoimmune disease. Various treatments have been tried to treat OLP but complete cure is difficult to achieve. Pimecrolimus is a new calcineurin inhibitor which can inhibit T-cell and mast-cell activation. We presented three cases of OLP patients treated with pimecrolimus 1% cream 2 times daily for 4 weeks. All of the lesions showed improvement with nearly complete remission. No side effects were observed during 6-12 months follow-up in all cases.

Key words : oral lichen planus; pimecrolimus; treatment

ผลของยาทาครีมไพมีโครลิมัส 1% ในการรักษารอยโรคไลเคนพลานัสในช่องปาก

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บทคัดย่อ

รอยโรคไลเคนพลานัสในช่องปาก เป็นรอยโรคที่เกี่ยวข้องกับการอักเสบของเนื้อเยื่ออ่อนและผิวหนังที่พบได้บ่อย สาเหตุการเกิดโรคยังไม่ทราบแน่ชัด แต่เชื่อว่าเป็นโรคที่เกี่ยวข้องกับภูมิต้านทานตนเองและที-เซลล์ มีรายงานการรักษารอยโรคไลเคนพลานัสในช่องปากด้วยวิธีต่าง ๆ แต่ยังไม่มีวิธีการใดที่สามารถทำให้รอยโรคหายขาดได้ ยาไพมีโครลิมัสเป็นยาตัวใหม่ที่ออกฤทธิ์ยับยั้งแคลซินิวริน ซึ่งสามารถยับยั้งการกระตุ้นที-เซลล์และมาส-เซลล์ ในรายงานฉบับนี้ได้กล่าวถึงการรักษาผู้ป่วยไลเคนพลานัสในช่องปากจำนวน 3 ราย ด้วยยาทาครีมไพมีโครมัส 1% วันละ 2 ครั้ง เป็นระยะเวลา 4 สัปดาห์ พบว่าผู้ป่วยทั้ง 3 รายมีอาการเจ็บลดลงและรอยโรคเกือบหายสนิท รวมทั้งไม่พบผลข้างเคียงจากการรักษาเมื่อติดตามผู้ป่วยไปในระยะเวลา 6-12 เดือน

คำสำคัญ : ไลเคนพลานัสในช่องปาก; ไพมีโครลิมัส; การรักษา

Introduction

Oral lichen planus (OLP) is a chronic mucocutaneous inflammatory disease that affects 0.5-2.2% of the population and is mainly found in women in their fifth or sixth decades of life.[1-3] The etiology is still unclear. The immunopathogenesis of OLP is complex, involving T-cells, mast cells, intercellular adhesion molecule-1 and HLA class II antigens[4-6] and may be associated with some drugs and dental materials.[7] Various clinical forms of OLP have been recognized. Reticular and plaque type of OLP are often asymptomatic. Whereas atrophic and erosive forms are often painful, interfere with patient's quality of life and require some treatments. Various treatments have been attempted to improve the symptomatic OLP. Corticosteroids in topical form are safe and effective treatments for OLP. The response rate has been reported to range from 30-70%.[8] Pimecrolimus is one of the new class of novel ascomycin immuno-modulating macrolactams, and has been developed for the treatment of inflammatory skin diseases such as atopic dermatitis, psoriasis and contact dermatitis.[9] The mechanism of the drug is inhibiting T-cell and mast-cell activation. Recently, there have been few reports using this medication in the treatment of OLP [10-12] but there were no reports of pimecrolimus in the treatment of Thai patients with OLP. side-effects The aim of the present study was to assess the efficacy and side-effects of pimecrolimus 1% cream in treatment of Thai patients with symptomatic OLP.

Case report

Three patients with atrophic OLP attending the Oral Medicine clinic, Faculty of Dentistry, Chulalongkorn University were asked to participate in the study. None of patients has systemic disease and taking systemic medication. Each subject gave written informed consent and the study was approved by Committee on Experimental Procedures Involving Human Subjects of the Faculty of Medicine, Chulalongkorn University Ethics Committee. Any topical medications previously prescribed for treatment of OLP were stopped for two weeks and systemic therapy for at least four weeks before starting this study. All the lesions were diagnosed by oral examination and confirmed by histopathology. The patients were instructed to apply pimecrolimus 1% cream (Elidel® , Novartis , Mexico) on dried lesions twice a day for four weeks. Transparent grids[13] were used to measure the size of erythematous lesions of the most severity area in mm^2, while discomfort scores were assessed using a visual analogue scale (VAS).[14] The OLP lesions were also evaluated before and after treatment to the criteria set by Thong-prasom et al.[15,16]

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

The first patient was a 67-year-old woman with atrophic lesion and white striaes at lower lip (Figure 1). Pimecrolimu 1% cream was administered topically twice daily for four weeks. The pain and the size of the lesion were evaluated. After four weeks, the patient reported 78.79% reduction of pain and almost complete absence of OLP (Figure 2). No side-effects were observed (Table1).

The second patient was a 35-year-old woman with an 11-year history of burning atrophic lesion at buccal gingival of all quadrant extended to mucobuccal fold. Pimecrolimus 1% cream was administered twice daily for four weeks. After four weeks of treatment, nearly complete disappearance of OLP lesion was documented and 62.22% reduction of burning sensation was reported. No side-effects were observed except the bad taste of the drug.

The third patient was a 28-year-old man with a history of 8-year burning sensation on the left and right buccal mucosa. Pimecrolimus 1% cream was administered topically twice daily on both buccal mucosa. After four weeks, the symptoms reduced 81.63% and only white hyperkeratotic striae was seen. No side-effects were observed.

Discussion

Various regimens have been tried to treat OLP but complete cure has been difficult to achieve. Corticosteroids are the first-line drugs for the treatment of OLP and are effective in managing symptomatic OLP. Fluocinolone acetonide 0.1% in orabase (FAO) has been shown to be more effective than triamcinolone acetonide 0.1% in orabase (TAO) with no serious side effects.[15] Moreover, the effectiveness of various forms of topical fluocinolone acetonide applications in patients with OLP in a 2-year treatment resulted in complete remission of 77.3%, 21.4%, and 17.0% of patients in the FAO, fluocinolone acetonide in solution (FAS), and FAS/FAO groups, respectively.[16]

Acute pseudomembranous candidiasis is the only common side-effect from topical corticosteroid which can be prevented or treated with topical antifungal agent.[15,17,18] Although there are some reports of systemic absorption and adrenal suppression from using super-potent topical steroids in treatment of skin disorders, but there has been no report about adrenal suppression from long term oral application of topical corticosteroids.[19-21]

Other immunosuppressive drugs such as cyclosporine and topical tacrolimus has been reported in treatment of OLP.[13,22-26] Cyclosporine is a polypeptide that inhibits the transcription of several cytokine genes, thereby suppressing T-cell cytokine production. Some studies have been reported benefit from applied cyclosporine topically or in form of mouth rinse[13,24] but others have reported little benefit or no significant improvement.[22,23] Cyclosporine may be used as an alternative therapy from conventional treatment of OLP but should not be use as a first drug of choice because of the high cost of long term treatment and the availability of effective alternatives. Severe side-effects of systemic cyclosporine, such as hypertension and nephrotoxicity, preclude its use for OLP.[7]

Tacrolimus is an immunomodulating agent inhibiting T-cell activation at 10-100 times lower concentration than cyclosporine.[27] This drug used topically to control symptoms and has been shown to be effective in treatment of OLP. However, local irritation is the most common side-effect.[25,26]

Pimecrolimus is a topical immuno-suppressant calcineurin inhibitors that is applied to many skin diseases such as atopic dermatitis, psoriasis and contact dermatitis.[9,28-30] It is related to tacrolimus and shares the same cellular binding targets and mechanism of action.[30] There are some reports about the efficacy of topical pimecrolimus when treating OLP lesions with adhesive ointment two times daily in patients with OLP. After four months, lesions nearly disappear and patients experience only a slight burning sensation immediately following the application of pimecrolimus.[10] Other studies have also been shown partial or complete remission in OLP patients treated with pimecrolimus 1% cream.[11,12]

Consistent to previous reports, in our study, improvement in both subjective and objective assessment occurred in all three patients treated with topical pimecrolimus 1% cream. Following the administration of pimecrolimus for four weeks, nearly complete resolution of OLP together with symptom improvement were documented in all patients. Moreover, there are no serious side-effects in all cases during 6-12 months follow-up.Therefore, pimecrolimus 1% cream has a potential role to be a novel alternative treatment of symptomatic OLP in patients who do not respond to conventional therapy. However, further studies, are also necessary to evaluate the relapse rate of patients with symptomatic OLP upon discontinuation of pimecrolimus therapy. Long term follow-up of topical pimecrolimus treatment in OLP should be considered both beneficial and unwanted effects.

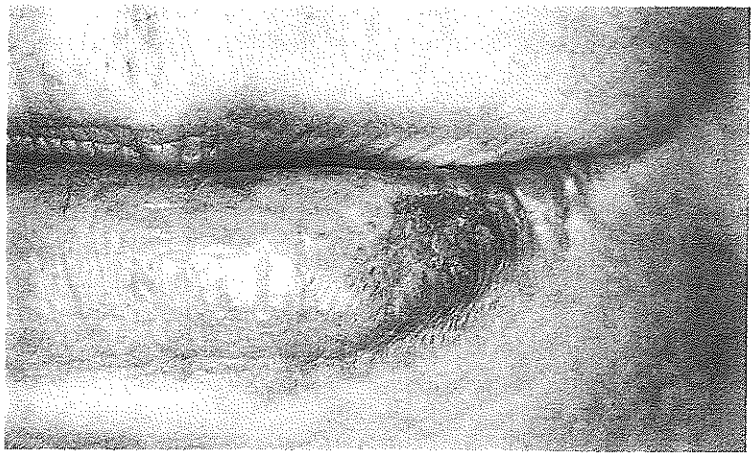

Figure 1 The first patient with atrophic OLP and white striae at lower lip

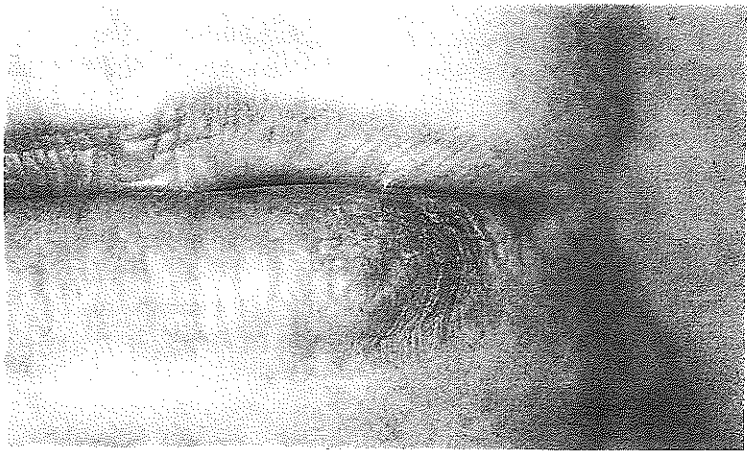

Figure 2 After 4 weeks of treatment with pimecrolimus 1% cream, the lesion was almost complete disappearance

Table 1 The VAS, clinical score and size of the erythematous lesion in each OLP subject before and after four weeks treatment with pimecrolimus 1% cream

	Before treatment			**After 4 weeks treatment**		
Subject	VAS (1-10)	Score (0-5)	Size (mm^2)	VAS (1-10)	Score (0-5)	Size (mm^2)
1	3.3	2	29	0.7	1	0
2	4.5	2	48	1.7	1	0
3	9.8	3	110	1.8	1	0

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References

1. Pindborg JJ, Mehta FS, Daftary DK, Gupta PC, Bhonsle RB. Prevalence of oral lichen planus among 7639 Indian villagers in Kerala, South India. *Acta Derm Venereol* 1972; 52: 216-20.
2. Silverman SJ, Gorsky M, Lozada-Nur F. A prospective follow-up study of 570 patients with oral lichen planus : persistence, remission, and malignant association. *Oral Surg Oral Med Oral Pathol* 1985; 60 :30-4.
3. Axell T, Rundquist L. Oral lichen planus-demograhic study. *Community Dent Oral Epidemiol* 1987; 15: 52-6.
4. Sugerman PB, Savage NW, Walsh LJ, et al. The pathogenesis of oral lichen planus. *Crit Rev Oral Biol Med* 2002; 13: 350-65.
5. Villarroel Dorrego M, Correnti M, Delgado R, Tapia FJ. Oral lichen planus: immunohistology of mucosal lesions. *J Oral Pathol Med* 2002 ; 31 :410-4.
6. Carrozzo M, Francia Di Celle P, Gandolfo S, et al. Increased frequency of HLA-DR6 allele in Italian patients with hepatitis C virus-associated oral lichen planus. *Br J Dermatol* 2001; 144: 803-8.
7. Lodi G, Scully C, Carrozo M, Griffiths M, Sugerman PB, Thongprasom K. Current controversies in oral lichen planus: Report of an international consensus meeting. Part2. Clinical management and malignant transformation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; 100: 40-51.
8. Eisen D. The clinical manifestations and treatment of oral lichen planus. *Dermatol Clin* 2003; 21: 79-89.
9. Gupta AK, Chow M. Pimecrolimus: A review. *J Eur Acad Dermatol. Venereol* 2003; 17: 493-503.
10. Dissemond J, Schroter S, Franckson T, Herbig S, Goos M. Pimecrolimus in an adhesive ointment as a new treatment option for oral lichen planus. *Br J Dermatol* 2004; 150: 782-4.
11. Esquivel-Pedraza L, Fernandez-Cuevas L, Ortiz-Pedroza G, Reyes-Gutierrez E, Orozco-Topete R. Treatment of oral lichen planus with topical pimecrolimus 1% cream. *Br J Dermatol* 2004; 150: 771-3.
12. Swift JC, Rees TD, Plemons JM, Hallmon WW, Wright JC. The effectiveness of 1% pimecrolimus cream in the treatment of oral erosive lichen planus. *J Periodontol* 2005; 76: 627-35.
13. Harpenau LA, Plemons JM, Rees TD. Effectiveness of a low dose of cyclosporine in the management of patients with oral erosive lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; 80: 161-7.
14. Scott J, Huskisson EC. Graphic representation of pain. *Pain* 1976; 2: 175-84.
15. Thongprasom K, Luangjarmekorn L, Sererat T, Taweesap W. Relative efficacy of fluocinolone acetonide compared with triamcinolone acetonide in treatment of oral lichen planus. *J Oral Pathol Med* 1992; 21: 456-8.
16. Thongprasom K, Luengvisut P, Wongwatanakij A, Boonjatturus C. Clinical evaluation in treatment of oral lichen planus with topical fluocinolone acetonide: a 2-year follow-up. *J Oral Pathol Med* 2003; 32: 315-22.
17. Carbone M, Conrotto D, Carrozzo M, Broccoletti R, Gandolfo S, Scully C. Topical corticosteroids in association with miconazole and chlorhexidine in the long-term management of atrophic-erosive oral lichen planus: a placebo-controlled and comparative study between clobetasol and fluocinonide. *Oral Dis* 1999; 5: 44-9.
18. Gonzalez-Moles MA, Morales P, Rodriguez-Archilla A, Isabel IR, Gonzalez-Moles S. Treatment of severe chronic oral erosive lesions with clobetasol propionate in aqueous solution. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; 93: 264-70.
19. Levin C, Maibach HI. Topical corticosteroid-induced adrenocortical insufficiency: clinical implications. *Am J Clin Dermatol* 2002; 3: 141-7.
20. Gilbertson EO, Spellman MC, Piacquadio DJ, Mulford MI. Super potent topical corticosteroid use associated with adrenal suppression: clinical considerations. *J Am Acad Dermatol* 1998; 38: 318-21.
21. Garden JM, Freinkel RK. Systemic absorption of topical steroids. Metabolic effects as an index of mild hyper-cortisolism. *Arch Dermatol* 1986; 122:1007-10.
22. Levell NJ, Macleod RI, Marks JM. Lack of effect of cyclosporin mouthwash in oral lichen planus. *Lancet* 1991; 337: 796-7.

23. Jungell P, Malmstrom M. Cyclosporine A mouthwash in the treatment of oral lichen planus. *Int J Oral Maxillofac Surg* 1996; 25: 60-2.
24. Eisen D, Ellis CN, Duell EA, Griffiths CE, Voorhees JJ. Effect of topical cyclosporine rinse on oral lichen planus. A double-blind analysis. *N Engl J Med* 1990 2; 323: 290-4.
25. Olivier V, Lacour JP, Mousnier A, Garraffo R, Monteil RA, Ortonne JP. Treatment of chronic erosive oral lichen planus with low concentrations of topical tacrolimus: an open prospective study. *Arch Dermatol* 2002; 138: 1335-8.
26. Kaliakatsou F, Hodgson TA, Lewsey JD, Hegarty AM, Murphy AG, Porter SR. Management of recalcitrant ulcerative oral lichen planus with topical tacrolimus. *J Am Acad Dermatol* 2002; 46: 35-41.
27. Bekersky I, Lilja H, Lawrence I. Tacrolimus pharmacology and nonclinical studies: from FK506 to protopic. *Semin Cutan Med Surg* 2001; 20: 226-32.
28. Kempers S, Boguniewicz M, Carter E, Jarratt M, et al. A randomized investigator-blinded study comparing pimecrolimus cream 1% with tacrolimus ointment 0.03% in the treatment of pediatric patients with moderate atopic dermatitis. *J Am Acad Dermatol* 2004 ; 51: 515-25.
29. Gribetz C, Ling M, Lebwohl M, et al. Pimecrolimus cream 1% in the treatment of intertriginous psoriasis: a double-blind, randomized study. *J Am Acad Dermatol* 2004 ; 51: 731-8.
30. Nghiem P, Pearsen G, Langley RG. Tacrolimus and pimecrolimus : from clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis. *J Am Acad Dermatol* 2002; 46: 228-41.