EFFICACY OF *CENTELLA ASIATICA* IN ORABASE IN THE TREATMENT OF ORAL LICHEN PLANUS AND ORAL LICHENOID LESIONS

KATTALEE KITTIPRASAN

A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF SCIENCE (ORAL MEDICINE)
FACULTY OF GRADUATE STUDIES
MAHIDOL UNIVERSITY
2005

ISBN 974-04-5946-3

Thesis
entitled

EFFICACY OF *CENTELLA ASIATICA* IN ORABASE IN THE TREATMENT OF ORAL LICHEN PLANUS AND ORAL LICHENOID LESIONS

Kattalee Kittiprasan

Miss Kattalee Kittiprasan
Candidate

Waranun Buajeeb

Assoc. Prof. Waranun Buajeeb,
B.Sc., D.D.S., M.Sc. (Oral Medicine),
Dip. Thai Board of
Oral Diagnostic Sciences,
Ph.D. (Oral Biology)
Major-Advisor

Supanee Thanakun

Asst. Prof. Supanee Thanakun,
D.D.S., Grad. Dip. in Clin.Sc.
(Oral Medicine), M.Sc. (Oral Medicine),
Dip. Thai Board of
Oral Diagnostic Sciences
Co-Advisor

Mullika Sirirat

Assoc. Prof. Mullika Sirirat,
D.D.S., Grad. Dip. in Clin.Sc.
(Periodontics),
Dip. Thai Board of Periodontology
Co-Advisor

Rassmidara Hoonsawat

Assoc. Prof. Rassmidara Hoonsawat,
Ph.D.
Dean
Faculty of Graduate Studies

Mullika Sirirat

Assoc. Prof. Mullika Sirirat,
D.D.S., Grad. Dip. in Clin.Sc.
(Periodontics),
Dip. Thai Board of Periodontology
Chair
Master of Science Programme in
Oral Medicine
Faculty of Dentistry

Thesis
entitled

EFFICACY OF *CENTELLA ASIATICA* IN ORABASE IN THE TREATMENT OF ORAL LICHEN PLANUS AND ORAL LICHENOID LESIONS

was submitted to the Faculty of Graduate Studies, Mahidol University

For the degree of Master of Science (Oral Medicine)

on

30 March, 2005

Kattalee Kittiprasan

Miss Kattalee Kittiprasan
Candidate

Pleumchitt Rojanapanthu

Assoc. Prof. Pleumchitt Rojanapanthu,
B.Sc. in Pharm,
M. Phil,
Ph.D. (Pharmaceutics)
Member

Waranun Buajeeb

Assoc. Prof. Waranun Buajeeb,
B.Sc., D.D.S., M.Sc. (Oral Medicine),
Dip. Thai Board of Oral Diagnostic Sciences, Ph.D. (Oral Biology)
Chair

Supanee Thanakun

Asst. Prof. Supanee Thanakun,
D.D.S., Grad. Dip. in Clin.Sc. (Oral Medicine), M.Sc. (Oral Medicine),
Dip. Thai Board of Oral Diagnostic Sciences
Member

Mullika Siriat

Assoc. Prof. Mullika Siriat,
D.D.S. Grad. Dip. in Clin.Sc. (Periodontics),
Dip. Thai Board of Periodontology
Member

Rassmidara Hoonsawat

Assoc. Prof. Rassmidara Hoonsawat,
Ph.D.
Dean
Faculty of Graduate Studies
Mahidol University

Theeralaksna Suddhasthira

Asst. Prof. Theeralaksna Suddhasthira,
B.Sc., D.D.S., Grad. Dip. in Clin.Sc. (Oral Surgery), Dip. Amer. Board of Oral and Maxillofacial Surgery,
Ph.D. (Biomedical Science)
Dean
Faculty of Dentistry
Mahidol University

ACKNOWLEDGEMENT

I would like to express my deep appreciation to Assoc. Prof. Waranun Buajeeb, my major advisor, for her valuable suggestion and guidance throughout this thesis.

I am very grateful to Assoc. Prof. Mullika Sirirat and Asst. Prof. Supanee Thanakun, my co-advisors, for their kind advice.

My gratitude also goes to Assoc. Prof. Pleumchitt Rojanapanthu, the external examiner from the Faculty of Pharmacology for *Centella asiatica* in orabase and placebo.

I would like to thank Mr. Somkit Susinrat, a pharmacist from Silom Medical Co.Ltd., for his co-ordination.

I am grateful to Miss Kamolrat Hiranrat and Miss Somsinee Tuntikul, my pretty friends, for their hearty assistance.

I wish to thank Miss Sasithon Seenu and Mr. Thammakit Jaipong, the staffs of the Department of Oral Medicine for their assistance.

I am appreciative of their kindness from other lectures, friends and persons that cannot specify all their names.

Finally, I would like to thank you the Faculty of Dentistry, Mahidol University for the grant in the academic year 2002 that giving me to complete this study.

Kattalee Kittiprasan

EFFICACY OF *CENTELLA ASIATICA* IN ORABASE IN THE TREATMENT OF ORAL LICHEN PLANUS AND ORAL LICHENOID LESIONS

KATTALEE KITTIPRASAN 4537001 DTOM/M

M.Sc.(ORAL MEDICINE)

THESIS ADVISORS: WARANUN BUAJEEB, Ph.D.(ORAL BIOLOGY), Dip.Thai Board of Oral Diagnostic Sciences, MULLIKA SIRIRAT, Dip. Thai Board of Periodontology, SUPANEE THANAKUN, Dip. Thai Board of Oral Diagnostic Sciences

ABSTRACT

Centella asiatica has an anti-inflammatory activity *in vivo*. It can also promote wound healing. This study aimed to compare the efficacy of *Centella asiatica* in orabase with triamcinolone acetonide in orabase 0.1% and placebo in the treatment of oral lichen planus and oral lichenoid lesions.

Forty-two patients with atrophic and/or erosive oral lichen planus or oral lichenoid lesions had their clinical diagnosis comfirmed by histopathologic examination and immunofluorescence. Patients with cutaneous lichen planus, pregnancy and lactation were excluded. Topical antifungals were prescribed for one month in patients with positive candidal culture at the beginning. Patients were ranked according to the severity of their lesions. On this basis, the patients were then evenly distributed into three groups. The three groups were given triamcinolone acetonide in orabase 0.1%, *Centella asiatica* in orabase or placebo, respectively. They were instructed to apply the medication on dried lesions four times a day. The severity of lesions and pain were assessed at the beginning, second week, and fourth week of treatment.

The results showed that the lesion severity was significantly improved in patients receiving triamcinolone acetonide in orabase 0.1% compared to that in patients receiving *Centella asiatica* in orabase or placebo. Pain was significantly relieved after treatment in all study groups. No statistically significant differences in the pain scores were found within the three study groups at the end of treatment. In conclusion, the efficacy of *Centella asiatica* in orabase was less than that of triamcinolone acetonide in orabase 0.1% in the treatment of oral lichen planus and oral lichenoid lesions.

KEY WORDS: ORAL LICHEN PLANUS/ ORAL LICHENOID LESIONS/ TRIAMCINOLONE ACETONIDE/ *CENTELLA ASIATICA*/ TREATMENT/ORABASE

103 P. ISBN 974-04-5946-3

ประสิทธิภาพของออราเบสใบบัวบกในการรักษาไลเคนพลานัสและรอยโรคไลเคนอยด์ในช่องปาก

(EFFICACY OF *CENTELLA ASIATICA* IN ORABASE IN THE TREATMENT OF ORAL LICHEN PLANUS AND ORAL LICHENOID LESIONS)

กัทลี กิตติประสาร 4537001 DTOM/M

วท.ม. (เวชศาสตร์ช่องปาก)

คณะกรรมการควบคุมวิทยานิพนธ์: วรานันท์ บัวจีบ, ปร.ด., อ.ท. วิทยาการวินิจฉัยโรคช่องปาก, มัลลิกา ศิริรัตน์, อ.ท. ปริทันตวิทยา, สุพานี ธนาคุณ, อ.ท. วิทยาการวินิจฉัยโรคช่องปาก

บทคัดย่อ

ใบบัวบกมีสมบัติต้านการอักเสบในสิ่งมีชีวิต และยังช่วยเร่งการหายของแผล การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาประสิทธิภาพของออราเบสใบบัวบกในการรักษาไลเคนพลานัสและรอยโรคไลเคนอยด์ในช่องปาก โดยเปรียบเทียบกับออราเบสไตรแอมซิโนโลน อะเซโทนายด์ร้อยละ 0.1 และยาหลอก

ทำการศึกษาในผู้ป่วยที่เป็นไลเคนพลานัสหรือรอยโรคไลเคนอยด์ในช่องปาก ชนิดฝ่อลีบและหรือชนิดถลอก จำนวน 42 คน ซึ่งได้รับการวินิจฉัยทางคลินิกและยืนยันผลด้วยการตรวจทางจุลพยาธิวิทยาและอิมมูโนฟลูออเรสเซนส์ ไม่ศึกษาในผู้ป่วยที่เป็นไลเคนพลานัสที่ผิวหนัง หญิงมีครรภ์ หรืออยู่ในระหว่างการให้นมบุตร ผู้ป่วยที่มีผลการเพาะเชื้อราเป็นบวกจะได้รับยาต้านเชื้อราเฉพาะที่เป็นเวลา 1 เดือน ก่อนเริ่มการรักษา จัดลำดับความรุนแรงของรอยโรคในผู้ป่วยแต่ละราย เพื่อจัดแยกผู้ป่วยออกเป็น 3 กลุ่มให้มีการกระจายความรุนแรงของรอยโรคเท่าๆกันในแต่ละกลุ่ม กลุ่มที่ 1, 2 และ 3 ได้รับการรักษาโดยออราเบสไตรแอมซิโนโลน อะเซโทนายด์ร้อยละ 0.1, ออราเบสใบบัวบก และยาหลอก ตามลำดับ แนะนำให้ผู้ป่วยทายาบนรอยโรคที่แห้งวันละ 4 ครั้ง ประเมินความรุนแรงของรอยโรคและอาการเจ็บปวดของผู้ป่วยเมื่อเริ่มการรักษาและภายหลังการรักษา 2 และ 4 สัปดาห์

ผลการศึกษาแสดงให้เห็นว่า ความรุนแรงของรอยโรคลดลงอย่างมีนัยสำคัญทางสถิติในกลุ่มผู้ป่วยที่ได้รับออราเบสไตรแอมซิโนโลน อะเซโทนายด์ร้อยละ 0.1 เมื่อเปรียบเทียบกับผู้ป่วยในกลุ่มที่ได้รับออราเบสใบบัวบกและยาหลอก อาการเจ็บปวดของผู้ป่วยภายหลังการรักษาลดลงอย่างมีนัยสำคัญทางสถิติในแต่ละกลุ่ม และไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติในระดับของความเจ็บปวดของผู้ป่วยทั้ง 3 กลุ่ม สรุปได้ว่าออราเบสใบบัวบกมีประสิทธิภาพต่ำกว่าออราเบสไตรแอมซิโนโลน อะเซโทนายด์ร้อยละ 0.1 ในการรักษาไลเคนพลานัสและรอยโรคไลเคนอยด์ในช่องปาก

103 หน้า ISBN 974-04-5946-3

CONTENTS

LIST OF TABLES

LIST OF FIGURES

Figure **Page**

LIST OF FIGURES (CONT.)

Figure **Page**

LIST OF ABBREVIATIONS

OLP	=	Oral lichen planus
OLL	=	Oral lichenoid lesions

CHAPTER I
INTRODUCTION

Background and significance of the study

Oral lichen planus (OLP) is one of the common oral diseases. (1, 2) OLP manifests in different forms, but the most common and most readily recognized form is white reticular. (3) OLP may occur with or without skin manifestration. (3) It is a cell-mediated immune response but the exact etiology is still unknown. (4-8) Whereas, OLP-like lesions which is called oral lichenoid lesions (OLL), have specific causes such as medication. (3, 9) The prevalence of OLL is approximate to OLP. (10, 11) Unfortunately, the differentiation between OLP and OLL is quite difficult. Therefore, the diagnosis of OLP and OLL often overlap.

OLP and OLL are chronic conditions which have both symptomatic and asymptomatic forms. (3, 12) The treatment of them is restricted to symptomatic lesions. (4, 12, 13) The principal therapy of OLP and OLL is the administration of topical or systemic corticosteroids. (12) Many adverse effects such as adrenocortical suppression, gastrointestinal irritation, osteoporosis and etc. are the limitation of systemic usage. (12) As the patients with OLP or OLL may have lesions for several years with exacerbation and remission periods (4), topical corticosteroids are more appropriate for the long term treatment.

Centella asiatica has many pharmacological properties such as anti-inflammatory activity, wound healing acceleration, ulcer-protective, psychoneuro-pharmacological, antimicrobial and antiviral effects. (14) The Faculty of Pharmacology, Mahidol University, has developed *Centella asiatica* in orabase for the treatment of oral lesions. Its toxicity has been studied in cell culture. The activity of *Centella asiatica* in orabase has not been studied in humans. If it can reduce severity of lesions and relieve pain in OLP and OLL patients without serious effects, it would be an alternative agent in the treatment of these diseases.

Hypothesis of the study

Centella asiatica in orabase can reduce lesion severity and relieve pain in patients with OLP and OLL.

Objective of the study

The purpose of this study was to compare the efficacy of *Centella asiatica* in orabase with triamcinolone acetonide in orabase 0.1% and placebo in the treatment of OLP and OLL.

Scope of the study

The patients with atrophic and/or erosive OLP or OLL in which diagnosis was confirmed by histopathologic examination and immunofluorescence were volunteers in the study. Patients with cutaneous lichen planus, pregnancy and lactation were excluded. Patients were ranked according to the severity of their lesions. On this basis, the patients were then evenly distributed into three groups. The three groups were given triamcinolone acetonide in orabase 0.1%, *Centella asiatica* in orabase or placebo, respectively. Patients were instructed to apply the medication on dried lesions four times a day. The severity of lesions and pain were assessed at the beginning, second week, and fourth week of study.

Benefits of the study

Centella asiatica in orabase can be used as an alternative agent in the treatment of OLP and OLL.

CHAPTER II
LITERATURE REVIEW

Lichen planus is a chronic inflammatory disease that can occur on oral mucosa or skin or both of them. (3, 12, 15, 16) The incidence of oral lesions, skin lesions, and both locations is 25%, 35%, and 40%, respectively. (16, 17, 18) Approximately 30% to 50% of patients with oral lesions have skin involvement. (15) About half of patients with skin lesions also have oral lesions. (16, 18, 19) The prevalence of OLP is 1-2% in the general population. (4, 6, 13, 20) OLP usually appears in adults, especially those 30-70 years old. (17, 18) In any way, there are also reports of the OLP arising in young adults and children. (4, 18) Furthermore, it affects females twice as frequently as males. (21)

Clinical features

The clinical characteristics of OLP are frequently multiple and bilateral lesions. (19) They predominantly involve on buccal mucosa (90% of cases), tongue (30%), and gingiva (13%). (21) Additionally, they may be seen on palate or lips. (21)

OLP can manifest in 6 different forms: reticular, papular, plaquelike, atrophic, erosive and bullous. (3, 13, 16) Many forms can present in one patient such as atrophy with reticular form. (2, 3, 4) Reticular, papular and plaquelike OLP are white lesions that cannot be rubbed off. (16) Reticular OLP, the most common and typical type, presents as a network of elevated white lines known as “Wickham’s striae”. (16, 17, 18) Papular OLP is small white raised lesions that can assemble in lines or plaques. (3, 17) Plaquelike OLP commonly appears as flat or elevated area on dorsum of tongue or buccal mucosa. (15) Patients with white lesions are often asymptomatic or may have slightly irritation. (1, 2, 15) Whereas, red lesions including atrophic, erosive, and bullous forms may be painful and may cause burning sensation due to hot or spicy foods. (16) Atrophic OLP is smooth diffuse erythema with or without white striae. (17, 19) Erosive OLP is granular and bright red lesion that may bleed producing pseudomembrane on lesional surface. (19) Bullous OLP is rare because it quickly

ruptures after its appearance. (15)The gingival lesions may be localized or generalized and usually occur on free and attached gingiva. (9) They may manifest as mild to intense erythema with ulcerations. (9) These pathognomonic features are commonly called desquamative gingivitis. (3, 4)

Cutaneous lichen planus generally occurs in adult aged 25 to 60 years. (21) It presents as 2-4 mm erythematous to violaceous papules or plaques. (4, 18, 20) They are flat-topped with an angular shape and may reveal white striae. (20) Their characteristic location is the flexor surface of forearms either as located lesions or in aggregate pattern. (21) Cutaneous lichen planus may cause pruritic symptom. (15, 17, 21) Generally, it is self-limiting disease that can disappear within 2 years. (17, 21) After resolution, it often has hyperpigmentation but can return to normal. (21) Moreover, lichen planus has been found in other sites: anogenital organs, scalp, nail, larynx, esophagus, and conjunctiva. (2, 4)

Etiology and pathogenesis

The exact etiology of OLP is still unknown. (3-8, 16, 22) Nevertheless, possible factors have been proposed such as infectious agents, trauma, allergies, and stress. (16, 21)

The basis of OLP pathogenesis is immunological mechanisms. (8, 21) There are extensive data suggesting that OLP represents cell-mediated immune response causing damage to basal keratinocytes. The immunological events may begin with the keratinocytes express foreign or altered self-antigen on their surface. These keratinocytes or infiltrate inflammatory cells secrete tumor necrosis factor-α (TNF-α) to induce Langerhans cells to migrate to draining lymph nodes. (6)

The mainly lesional lymphocytic infiltration of OLP is composed of T-cells (4, 8, 17, 21, 22, 23), including CD4+ and CD8+ T-cells. (8, 20) B cells and plasma cells are present in low numbers (4, 8) and natural killing cells are rarely present. (8)

CD4+ T-cells play a role before CD8+ T-cells by receiving antigen from Langerhans cells. They migrate to the inflammatory sites by TNF-α, interferon-gamma (IFN-γ) and other cytokines. In particularly, TNF-α and IFN-γ induce the expression of adhesion molecules including intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) on the endothelial lining of blood vessels in the affected oral mucosa. In addition, TNF-α and IFN-γ will induce keratinocyte

expression of ICAM-1 which allows T-cells to adhere to the keratinocytes and helps lymphocyte invasion within epithelium. (6)

Subsequently, the basal keratinocytes become the target of cell-mediated immune destruction. (4, 6, 8, 21, 22, 23) However, the responsible antigens and the mechanisms by which CD8+ T-cells induce apoptosis are unknown. (4, 23)

Diagnosis

The history of chronic multiple lesions and typical oral lesions are usually sufficient to make a clinical diagnosis of OLP. (4) Moreover, presence of skin lesions may be helpful. Occasionally, diagnostic problem can occur due to atypical lesions. Hence, the oral biopsy for histopathologic and immunofluorescent studies is the considerable procedure to confirm the diagnosis. (21)

The histopathologic features of OLP have been variably described in several reports. However, the two indispensable criteria are liquefying degeneration of basal cells and band-like zone of lymphocytic infiltration. Additionally supportive features for diagnosis of OLP are saw-tooth rete ridges, hyperkeratosis, subepithelial eosinophilic amorphous band and civatte bodies. (24) Furthermore, WHO has just included the absence of epithetial dysplasia in diagnostic criteria of OLP to exclude dysplastic lesions. (25)

The direct immunofluorescence is helpful to confirm diagnosis when routine histopathologic study is inconclusive. (1) The characteristic feature in OLP is fibrin deposits along basement membrane zone with a fibrillar pattern. (26) They are seen in 97% of OLP specimen. (26) Some cases show immunoglobulin G (IgG), IgA, IgM, and fibrinogen as globular structures in the deeper part of epithelium. Complement 3 deposits are sometime found in basement membrane zone. Similar globular staining of IgG, IgA, IgM and complement can also be seen in other mucocutaneous diseases including lupus erythematosus, erythema multiforme, and mucous membrane pemphigoid. (3) So, immunofluorescence alone is not adequate for diagnostic establishment of OLP. (3, 19)

The definitive diagnosis of OLP is based on a combination of characteristic clinical findings, history, and histopathology. (27) However, the histopathologic features of gingival OLP sometime are not classical according to plaque-induced gingivitis. (21) Furthermore, gingival OLP presenting as desquamative gingivitis is

possibly similar to other mucocutaneous diseases such as mucous membrane pemphigoid and pemphigus vulgaris. (2, 9, 21) In such cases, direct immunofluorescence is essential for definitive diagnosis of OLP.

Management

Since OLP is a chronic condition, the clinical management aims to relieve pain, eliminate erosions/ulcers and reduce risks of malignant development. (28) The mainstay of OLP therapy has been the administration of topical or systemic corticosteroids. The use of systemic corticosteroids is limited as their adverse effects. So, potent topical corticosteroids have been increasing prescribed in the OLP treatment. (29) An algorithm for the common management of OLP is as follows. (20, 30)

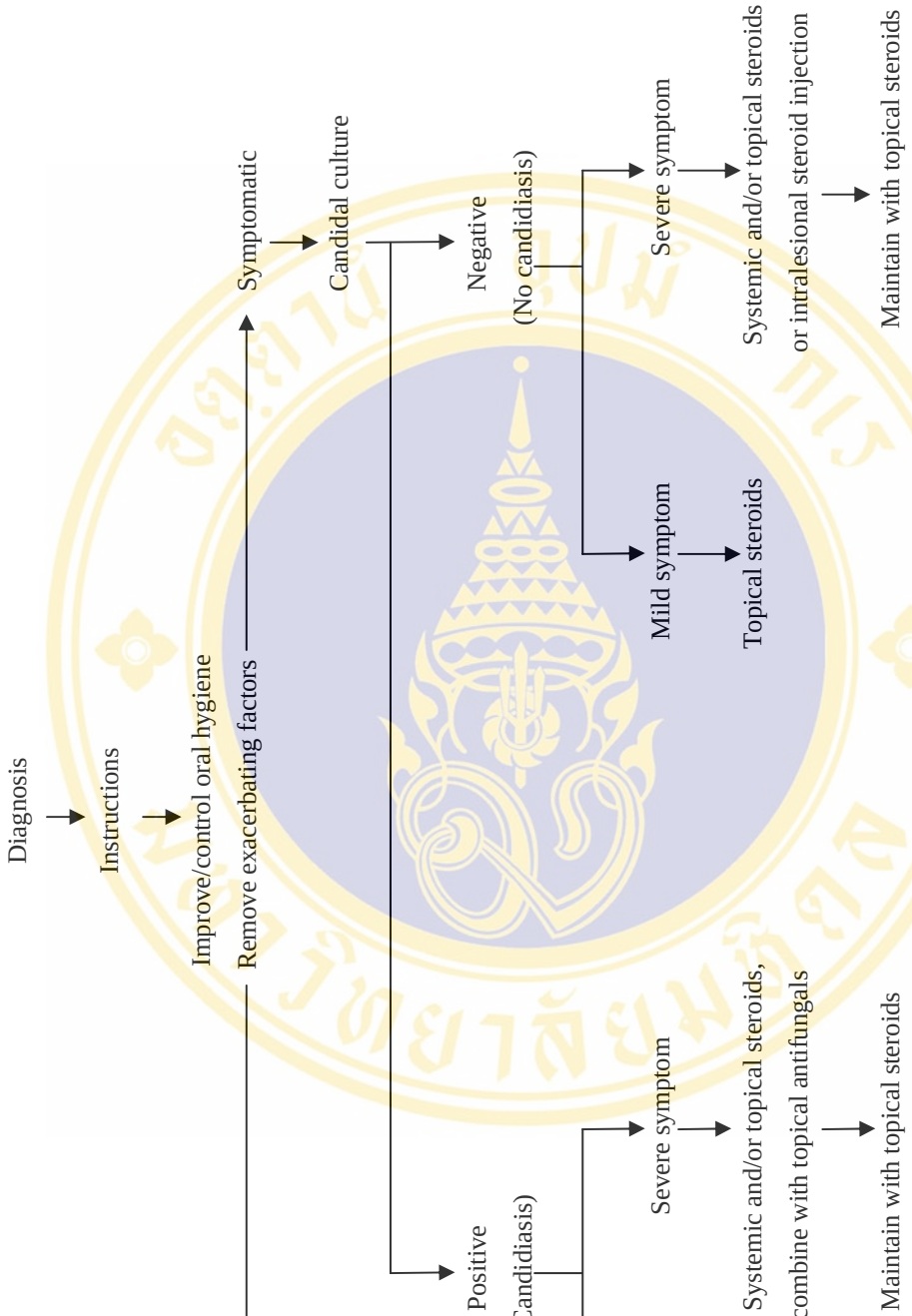


Figure 1. Algorithm for the management of OLP

Instructions to all OLP patients are the essence of OLP management. (Fig. 1) The initial management of OLP should include an improvement of oral hygiene and a removal of exacerbating factors. (Fig. 1) There are particular problems when atrophic or erosive/ulcerative OLP are present. Because toothbrushing may be complicated by gingival pain and bleeding. This situation frequently results in plaque accumulation that may adversely influence the course of OLP. Thereby, oral hygiene procedures in OLP patients must be effective to decrease discomfort and severity of the lesions. (21)

In all OLP patients, the local exacerbating factors should be removed. (13) Periodontal treatment should be performed. Teeth adjacent to OLP lesions which have sharp cusps or edges should be reduced. Corrosive amalgam fillings should be removed and replaced with non-amalgam filling. Removable prostheses with sharp areas should be polished. (4, 13) Moreover, psychological stress and anxiety that has been linked to OLP exacerbation should be relieved. (4)

In general, OLP patients with asymptomatic lesions do not require treatment. (19,21) However, form, size, and location of lesions should be recorded. Likewise, the diagnosis should be established and informed to patients. The biannual examination should be done to check on the course of disease. (19)

OLP patients with symptomatic lesions ranging from episodic pain to severe discomfort require active treatment. (15) Furthermore, symptoms may be exacerbated by candidal overgrowth or infection. Corticosteroids and other immunomodulators used in OLP therapy also predispose to candidal infection. (21)

Generally, oral candidal infections are seen in young, old, and sick individuals. (31) However, *Candida* can be identified as a commensal flora in the oral cavity of up to 40% of healthy individuals. (32) The most dominant species of *Candida* that is isolated from the oral cavity both in health and disease is *Candida albicans*. (31, 32) A number of reports showed that the mean carriage rate of *Candida albicans* for healthy individuals (no known underlying disease) was 17.7% (range; 1.9-62.3%). Whereas, mean carriage rate in hospitalized individuals (without clinical candidiasis) was 40.6% (range; 6.0-69.6%). (31) These data indicated that the health of individuals is a predisposing factor of *Candida albicans* colonization. Other factors that can increase *Candida* carriage are acidic saliva, smoking, and taking broad-spectrum antibiotics. (31)

Host defenses, strains of *Candida*, and candidal adhesion can effect candidal infection. (31) Other predisposing factors including local and general factors also increase candidal infection. Local factors that have been proposed are unhygienic or ill-fitting dentures, orthodontic appliances and tobacco smoking. (32, 33) Patients receiving broad-spectrum antibiotics, corticosteroids, or cytotoxic therapy and patients with diabetic mellitus, xerostomia, severe nutritional deficiencies and immunosuppressive diseases such as AIDS are more prone to oral candidiasis. (32)

The candidal culture should be performed so that the proper management can be planned. Anti-fungal treatment can decrease discomfort in OLP patients with secondary candidiasis. (21) As topical corticosteroids are generally considered to be the mainstay of treatment in mildly to moderately symptomatic OLP (15), mild cases of OLP with candidiasis, should be treated with topical antifungals together with topical corticosteroids. (34) For severe cases of OLP with candidiasis, the standard treatment should be systemic corticosteroids and/or topical corticosteroids in combination with topical antifungals. (21) When the lesions and symptoms relieve, the dosage of systemic corticosteroids should be tapered off and discontinued. (19) Maintenance therapy with topical corticosteroids is required. (Fig. 1)

Mild cases of OLP without candidiasis can be managed successfully with topical corticosteroids after meals and at bedtime. (19) For OLP patients with widespread lesions and severe symptom, the management with the burst of systemic corticosteroids will alleviate both pain and severity of the lesions. (Fig. 1) If localized ulcerative lesions do not respond to topical agent or locate on tongue, intralesional corticosteroids may be useful. (2, 12)

Recently, there is still a controversy as to whether OLP has malignant transformation. (1, 4, 21, 34, 35, 36) Studies on the aspect reported the range of malignant transformation of OLP per years was 0% to 12.5%. (34) However, the malignant transformation rate in the majority of studies is 0.5%-2% per year. (37) A number of studies from several countries indicating malignant transformation of OLP are shown in Table I.

Table I. A number of studies on the possible malignant transformation of OLP

Authors	Year	Country	No.of OLP patients	% of Bx-comfirmed Dx of OLP	No.of cancer patients	MTR (%)	Mean F/U (y)	OLP form/cancer	OLP site/cancer
Silverman *et al* (38)	1991	USA	214	100%	5	2.3	7.5	3 erosive, 1 atrophic, 1 reticular	2 tongue, 2 gingiva, 1 buccal
Voute *et al* (39)	1992	The Netherlands	113	100%	3	2.7	7.8	2 erosive, 1 reticular	1 lower lip, 1 tongue&buccal, 1 buccal
Barnard *et al* (37)	1993	UK	241	100%	9	3.7	no report	2 plaque, 5 erosive, 1 plaque&atrophic, 1 reticular&erosive	6 tongue, 1 vestibule, 1 alveolar ridge, 1 buccal
Silverman *et al* (40)	1997	USA	95	80%	3	3.2	6.1	no report	no report
Mignogna *et al* (41)	2001	Italy	502	100%	24	3.7	no report	22 reticular-plaque, 2 atrophic-erosive	9 tonque, 8 buccal, 3 gingiva, 2 tuberculosity, 1 palate, 1 gingiva/tuberculosity
Eisen (1)	2002	USA	723	100%	6	0.8	4.5	4 erosive, 2 atrophic	2 tongue, 2 gingiva, 1 buccal, 1 floor of mouth
Gandolfo *et al* (35)	2004	Italy	402	100%	9	2.2	4.9	3 atrophic-erosive, 2 atrophic 2 plaque&atrophic, 1 reticular&atrophic 1 reticular&plaque	4 tongue, 4 buccal, 1 vestibule
Rodstrom *et al* (36)	2004	Sweden	1028	62%	5	0.5	6.8	all of erythematous or ulcerative	3 buccal, 1 floor of mouth, 1 mucosa frontal part of inferior vestibulum

Bx = biopsy, Dx = diagnosis, MTR = malignant transformation rate, F/U = follow up
OLP form/cancer = OLP form at cancer development, OLP site/cancer = OLP site at cancer development

The variability of malignant transformation rate of OLP possibly results from differences in diagnostic criteria, time of follow-up and information on exposure to known oral carcinogens. The diagnostic criteria are major problem as there is no accepted standard. (34) Although the definitive diagnosis of OLP is based on a combination of characteristic clinical findings, history and histopathology. (27) But some cases of purported malignant transformation of OLP lacked histopathologic evidence.

Diagnostic failure may arise from clinicians and/or pathologists. Lack of adequate knowledge and experience to diagnose oral mucosal diseases and lack of initial biopsy for diagnostic confirmation are important errors of clinicians. Significantly, biopsy may be performed at several sites of OLP lesions to represent histopathological features of the entire lesions. (42)

In general, diagnosis is not a problem, if classically histopathological features are present. The pathologists may bias to diagnose OLP, as it is more common than other mucosal diseases. So, other conditions such as allergy, lichenoid drug reactions and lichenoid dysplasia are possibly included in the diagnosis of OLP. Lichenoid dysplasia was defined as a distinct histopathologic entity. This has histopathological features that revealed the characteristics of OLP and the additional presence of dysplasia within the overlying epithelium. However, the validation of this term has not been published yet. (25)

At present, OLP is classified as a precancerous condition. (43) This condition was defined as a generalized state associated with a significantly increased risk of cancer. (44) Because malignant transformation of OLP is prevalent among erythematous lesions, so their impaired mucosae possibly are damaged from carcinogenic agents. (45) Two reports indicated that tobacco and heavy alcohol use seem to be not related to OLP patients, as none of them who developed cancer were smokers or drinkers. (1, 45) However, OLP patients should be advised to stop smoking and alcohol consumption. (4) It has been suggested that extrinsic factors such as *Candida albicans* may play a role. It has been hypothesized that strains of *Candida albicans* are able to catalyze a carcinogen, *N*-nitrobenzylmethylamine. (45) Herpes simplex virus and human papillomavirus have also been implicated as risk factors in oral carcinogenesis. (1, 21)

As stated earlier, a careful and thorough examination is necessary. OLP lesions should be evaluated at each appointment. When the lesions show suspicious signs of malignant change such as non-healing ulcer, lack of homogeneity in the keratotic area, an additional biopsy and carefully histopathologic analysis must be performed. (41)

Treatment

As exacerbation in OLP patients is unpredictable and common, treatment is directed to symptomatic relief. (46) The currently available treatment is not specific or universally successful and may have local and/or systemic side effects. High-potency topical corticosteroids in an adhesive medium appear to be the safest and most effective treatment. For severe lesions, systemic and/or intralesional steroids could be used. Adjuvant agents such as antimycotics may be useful. (12)

Several medications have been used in the treatment of OLP. A wide list of OLP treatments is as follows.

Table II. Principal treatment modalities of OLP

1. Corticosteroids
1.1 Topical
Betamethasone phosphate 0.05%
Batamethasone valerate 0.1%
Clobetasol proprionate 0.05%
Fluocinolone acetonide 0.025%, 0.1%, 0.2%
Fluocinonide 0.05%
Fluticasone proprionate 0.005%, 0.05%
Hydrocortisone hemisuccinate 0.25-2.5%
Triamcinolone acetonide 0.025%, 0.1%, 0.5%
1.2 Systemic
Prednisone 1, 2.5, 5, 10, 20, 50 mg
Prednisolone 5 mg
Methylprednisolone 2, 4, 8, 16, 24, 32 mg

2. Retinoids
2.1 Topical
Isotretinoin 0.1%
Retinoic acid 0.05%
Tretinoin 0.1%
2.2 Systemic
Acitretin 10mg
Etritinate 25 mg
Isotritinoin 10 mg
Temarotene 800 mg
Tretinoin 10 mg

3. Immunosuppressive agents
3.1 Topical
Cyclosporine 25, 100 mg/mL
Tacrolimus 0.03%, 0.1%, 0.3%
3.2 Systemic
Azathioprine 50 mg
Cyclosporine 25, 50, 100 mg

4. Antimicrobials
Amphotericin B 10 mg
Dapsone 50 mg
Griseofulvin 500 mg
Hydroxychloroquine 200 mg
Interferon 3-10 million IU thrice
Tetracycline 100, 250 mg

5. Others
Enoxaparin 3 mg SC
Levamisole 50 mg
Phenytoin 100 mg
Photochemotherapy
Surgery
Thalidomide 150 mg

1. Corticosteroids

Corticosteroids are the most effective anti-inflammatory agents available. (47)They can inhibit many of the processes associated with inflammation and the immune response. In early stages, they reduce the capillary permeability caused by histamine and bradykinin, which in turn reduces edema. They also inhibit both bradykinin formation and the migration of white blood cells into the site of inflammation. In later stages, steroids reduce granulation-tissue formation by inhibiting the proliferation of fibroblasts and blood vessels. (48)

Steroids are widely used in the treatment of recurrent oral ulceration and other oral mucosal lesions such as OLP, erythema multiforme, and pemphigus. Whereas, other lesions caused by infection are contraindication of steroids. It should be remembered that using steroids to suppress inflammation is only palliative but the underlying cause of the inflammation still remains. (48)

Currently, steroids are the mainstay of treatment of OLP. (4, 21, 46) They are administered topically, intralesionally or systemically.(4) Mildly to moderately symptomatic OLP are treated by topical applications. (49) Best results are achieved when the period of contact between steroids and lesions is maximal. (48) Whereas, patients with moderately to severely symptomatic OLP or unresponding to topical therapy may require systemic steroids. (49) In some instances, a persistent localized lesion may benefit from a steroid injection. (48, 49)

1.1 Topical corticosteroids

Available agents are numerous and variable in potency relative to the natural corticosteroid hydrocortisone. (49) Some trials of the topical corticosteroids in the treatment of OLP are shown in Table III.

Table III. Topical corticosteroids in the treatment of OLP

Drug	Author	Year	Study type	Pts. (no.)	Dur. (wks)	Results (%) CR	PR	No R
I. Very high potency								
Clobetasol proprionate 0.05%	Lozada-Nur *et al* (50)	1991	open	9 (e)	2	55.6	22.2	22.2
	Rodstrom *et al* (51)	1994	double-blind, comparative	17 (e)	9	71	no report	
	Carbone *et al* (52)	1999	placebo-controlled, comparative	20 (e/a)	24	75	25	-
	Carbone *et al* (53)	2003	comparative	23 (e/a)	24	69.6	26	4.4
II. High potency								
Fluocinolone acetonide 0.1%	Thongprasom *et al* (54)	1992	comparative	19 (e/a)	4	68.4	31.6	-
	Buajeeb *et al* (55)	1997	comparative	18 (e/a)	4	56	no report	
Fluocinonide 0.05%	Voute *et al* (56)	1993	double-blind, placebo-controlled	20 (e/a)	9	20	60	20
	Carbone *et al* (52)	1999	placebo-controlled, comparative	20 (e)	24	25	75	-

Pts. = Patients; no. = number(s); Dur. = Duration; wks = weeks

CR = complete response; PR = partial response; No R = No improvement or worsening of lesions

e = erosive OLP; e/a = erosive and atrophic OLP

Table III. Topical corticosteroids in the treatment of OLP (continued)

Drug	Author	Year	Study type	Pts. (no.)	Dur. (wks)	Results (%) CR	PR	No R
III. Medium potency								
Betamethasone phosphate 0.5 mg tablet dissolved in 10 mL water	Hegarty *et al* (57)	2002	crossover	22 (e/a)	6*	41% reduction in the mean surface area of lesions		
Betamethasone valerate 800 µg daily	Tyldesley and Harding(58)	1997	placebo-controlled	11 (e/a)	8	(66.7 (50	- 50	33.3)** -)***
Fluticasone proprionate 50 µg aqueous solution	Hegarty *et al* (57)	2002	crossover	22 (e/a)	6*	63% reduction in the mean surface area of lesions		
Triamcinolone acetonide 0.1%	Thongprasom *et al* (54)	1992	comparative	19 (e/a)	4	42.1	57.9	-
	Rodstrom *et al* (51)	1994	double-blind, comparative	17 (e/a)	9	71	no report	
IV. Low potency								
Hydrocortisone 0.3%	Holbrook *et al* (59)	1998	open	53 (all)	2-4	49	38	13

Pts. = Patients; no. = number(s); Dur. = Duration; wks = weeks

CR = complete response; PR = partial response; No R = No improvement or worsening of lesions

e/a = erosive and atrophic OLP, all = all types of OLP

* = before wash out period; ** = of the 9 patients with minor erosive form,

*** = of the 2 patients with non erosive form

However, commonly prescribed steroids are triamcinolone acetonide 0.1% in orabase or ointment, betamethasone valerate 0.1% cream or ointment, fluocinonide 0.05% gel or ointment, fluocinolone acetonide 0.1% in orabase, dexamethasone 0.5 mg/mL elixir, and clobetasol proprionate 0.05% gel, cream, or ointment. (49) Adhesive preparations are widely used, even though there are no any controlled studies showing that topical steroids in adhesive bases are more effective than creams or ointment. (12) Topical steroids are typically prescribed to be applied to lesions with a thin layer after each meal and at bedtime. When the symptoms and severity of lesions improved, the dosage should be decreased as necessary to control disease. (49)

The choice of a given steroid depends on lesional presentation, patient preference, and clinician experience. For localized lesions, oral paste or gel are commonly prescribed. Whereas, widespread lesions, mouthwash or oral solution is more appropriate than paste. For gingival OLP, using custom tray or mouthguard to deliver the drug may be especially useful. The patient should wear it with ointment or gel for 30 minutes after meals and at bedtime. (49)

Because symptomatic OLP must be treated, using topical steroids on atrophic and erosive/ulcerative lesions can change those lesions to reticular form. Moreover, topical steroids have been used with some success to convert plaques into reticular lesions. (28)

All currently available topical steroids are absorbed into the systemic circulation and therefore have some systemic effects, although this is considerably less than those seen with systemic steroids. The occurrence and severity of side effects depend on the duration of use, dosage, dosing regime and specific drug used, along with individual variability. However, the highest risk factor appears to be prolonged use. (47) Topical steroids may induce mucosal atrophy and predispose to candidal superinfection. (49) Patient instructions on drug use may help to reduce these side effects.

In denture wearers and xerostomics, candidal culture should be done to ensure that they do not have a pre-existing candidiasis. (4) Moreover, candidal culture should therefore be done routinely in patients who require potent steroids. (16) Prevention by adding antimycotic therapy is helpful for these cases. (12)

Current data suggest that adrenal suppression is not a significantly side effect for the long term use of topical steroids. (12) However, when use in large amounts for

prolonged periods or with gingival stent, absorption is greatly increased and may lead to adrenal suppression. (3, 15)

Although topical steroids are commonly prescribed, the failure of use occasionally occurs due to the difficulty and frequency of application. In OLP patients who have multiple lesions or severe symptoms that do not response to topical treatment, adjuvant or alternative treatment is required. (46)

1.2 Intralesional steroids

Intralesional steroids that have been used include triamcinolone acetonide, dexamethasone, hydrocortisone, and methyl prednisolone. (21) They are often administered with topical and/or systemic steroids. Zegarelli (60) injected methylprednisolone 40 mg/mL combined with triamcinolone acetonide in orabase for treating seven patients with erosive/ulcerative OLP. Five patients had a 100% clinical improvement; one patient had a 75% clinical improvement and one was considered 25% or merely mild improvement at the end of three week treatment period. However, triamcinolone acetonide is generally used for intralesional therapy in ulcerative OLP. (2) Subcutaneous injection of 0.2-0.4 mL of a 5-10 mg/mL triamcinolone acetonide at weekly or twice weekly intervals over 3-4 weeks can be effective to induce the healing of recalcitrant or extensive lesions. (2, 15)

Long-standing erosions especially in a frequently traumatized area like the tongue, may respond best to intralesional injection. (12) Whereas gingival OLP is not appropriate for this technic. Because it is usually impossible to inject significant quantities of steroids into the gingiva. (60)

1.3 Systemic corticosteroids

Available agents are variable in potency as shown in Table IV. (61, 62)

Table IV. Glucocorticoid potencies and half-life

Glucocorticoids	Half-life	
	Plasma (minutes)	Biologic (hours)
I. Short-acting		
Cortisone 5, 10, 25 mg	30	8-12
Hydrocortisone 5, 10, 20 mg	80-118	8-12
II. Intermediate-acting		
Prednisone 1, 2.5, 5, 10, 20, 50 mg	60	18-36
Prednisolone 5 mg	115-212	18-36
Triamcinolone 4, 8 mg	200+	18-36
Methylprednisolone 2, 4, 8, 16, 24, 32 mg	78-188	18-36
III. Long-acting		
Dexamethasone 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6 mg	110-210	36-54
Betamethasone 0.6 mg	300+	36-54

Common systemic steroids are prednisone, prednisolone, or methylprednisolone. (12) Because of the adverse effects, their use is reserved for patients with acute exacerbation, multiple ulcerations, or widespread lesions. Adverse effects are common even after a course as short as two weeks. (16) The adverse effects include skin and muscle atrophy, delayed wound healing and increased risk of infection, behavioral changes, hypertension, peptic ulcers and gastrointestinal bleeding, Cushing's syndrome and diabetes. (47) Therefore, the approach to therapy is to prescribe a high-dose, short course regimen to maximize therapeutic effect while minimizing side effects. (49) When the lesions are well into remission, the dosage of systemic steroids may be tapered off and discontinued. If small isolated lesion still presented, these can be managed with topical steroids. (19)

Short- or intermediate-acting steroids should be given as a single dose in the morning (before 9 AM). Because it is likely to produce fewer side effects and less

pituitary-adrenal suppression than a divided dosage regimen with the same agent or an equivalent dosage of a long-acting agent. Also, alternate day therapy with intermediate-acting agents further reduces the prevalence and degree of side effects. (62) Systemic steroids may be taken with food, milk, or an antacid to minimize stomach upset. The dosage requirements are variable and must be individualized. (61) The ultimate dosage chosen depends on the severity of lesions and the patient's weight. (49) Moreover, dosage should be modified on the basis of the patient's response to treatment. When systemic steroids are prescribed for periods of longer than two weeks, their dosage must be withdrawn gradually. (15) Too rapid withdrawal of long-term therapy can cause acute adrenal insufficiency that resulting in fever, myalgia, arthralgia, and malaise. Additionally, adrenally suppressed patient cannot respond to stress. (62)

Systemic steroids are often used in combination with topical steroids or azathioprine to reduce their dosage and side effects. (19, 60, 63) Zegarelli (60) used oral prednisone combined with triamcinolone acetonide in orabase in five patients with erosive/ulcerative OLP. Prednisone was administered in the following manner: 30 mg/d for the first week, 15 mg/d for the second, and 5 mg/d for the third and final week of treatment. Triamcinolone acetonide in orabase was applied to the affected sites four times a day for at least three weeks. After three weeks, Two of these five healed completely (100%), one showed a 75% improvement and two were graded 50% improved. Lozada (63) used oral prednisone and oral azathioprine in four OLP patients. The type of OLP was not reported. The minimum effective dose of prednisone was defined as the lowest amount of drug which would completely control signs and symptoms. All OLP patients were started on 40 mg/d prednisone and 50 mg azathioprine every other day. The doses were adjusted on the basis of adverse effects and clinical response. The follow-up periods were 1, 1.5, 2 and 16 months, respectively. After follow-up period, only the patient with 16 months follow-up had a complete remission, whereas the others had a partial remission. Carbone *et al* (53) used 50 mg/d prednisone and afterwards with clobetasol ointment in an adhesive medium plus antimycotics in twenty-two patients with atrophic-erosive OLP. When an almost 50% reduction in lesion size was achieved, the prednisone dose was tapered to 25 mg/d for a week, then to 12.5 mg/d for a week, and finally to 6 mg/d for the last

week. Clobetasol proprionate was initially applied twice daily, then once daily for a total period of 6 months. All patients received concomitant antimycotic treatment. After six months of therapy, 68.2% of patients had complete remission, 22.7% showed partial remission, and 9.1% had no beneficial response to the treatment.

When patients receive high-dose steroids for a long time, they may develop Cushing's syndrome. Cushing's syndrome includes moon face, buffalo hump, central obesity, easy bruising, acne, hirsutism and striae. Furthermore, prolonged therapy with systemic steroids can lead to suppression of pituitary- adrenal function. (62) So, these patients should be monitored hematologic function regularly. (16)

The use of systemic steroids is contraindicated in patients with systemic fungal infections except as maintenance therapy in adrenal insufficiency. They should be used with caution in patients with pregnancy, diabetes mellitus, osteoporosis, peptic ulcer, esophagitis, hypertension, hypothyroidism, immunization, hypoalbuminemia, psychosis, and liver disease. (62)

2. Retinoids

The retinoids have anti-inflammatory properties, perhaps through their interactions with the arachidonic acid cascade; they stimulate macrophage activation and antibody-dependent cell-mediated cytotoxicity. Moreover, retinoids may also reduce the CD4+ lymphocyte infiltrate and increase the macrophages in OLP lesion, thus accelerating the healing process. For this reason retinol and its synthetic and natural analogues (retinoids) may be useful in the treatment of OLP. (12)

Some trials of retinoids in the treatment of OLP are shown in Table V.

Table V. Retinoids in the treatment of OLP

Drug	Author	Year	Study type	Pts. (no.)	Dur. (wks)	Results
I. Topical retinoids						
Retinoic acid 0.05%	Buajeeb *et al* (55)	1997	comparative	15 (e/a)	4	7 patients (47%) improved.*
Tretinoin 0.1%	Sloberg *et al* (64)	1979	placebo-controlled	23 (e/a)	8	71% of atrophic and erosive lesions had improved. Other lesions were unchanged.
Isotretinoin 0.1%	Giustina *et al* (65)	1986	double-blind	11 (all)	8	10 patients (90%) showed improvement.
II. Systemic retinoids						
Etretinate 75 mg/d	Hersle *et al* (66)	1982	comparative, double-blind	17 (all)	8	90% of atrophic-erosive lesions improved. 100% of plaque-reticular lesions improved.
	Gorsky and Raviv (67)	1992	open	5 (nr)	8	All patients (100%) had improved.
Isotritinoin (13-cis-retinoic acid) 10-60 mg/d	Camisa and Allen (68)	1986	open	5 (e)	8	3 patients (60%) had definite improvement. 1 patient (20%) had slight improvement. 1 patient (20%) had no change.

Pts.= Patients; Dur.= Duration; wks= weeks

e/a = erosive and atrophic OLP; all = all types of OLP; nr = no report type; e = erosive OLP

Table V. Retinoids in the treatment of OLP (continued)

Drug	Author	Year	Study type	Pts. (no.)	Dur. (wks)	Results
II. Systemic retinoid						
Temarotene 800-4800 mg/d	Bollag and Ott (69)	1989	open	3 (nr)	17-63	All patients (100%) had improved.**
Acitretin 30 mg/d	Laurberg *et al* (70)	1991	double-blind	30 (mu)	8	19 patients (64%) had a remission or marked improvement.
Tretinoin (all-trans-retinoic acid) 10-30 mg/d	Ott *et al* (71)	1996	open	18 (va)	6.8-133	13 patients (72%) had a complete remission. 4 patients (22%) had a marked improvement.

Pts. = Patients; Dur. = Duration; wks = weeks

nr = no report type; mu = mucocutaneous lichen planus; va = various form of lichen planus

** = One patient (33.3%) had complete response, 1 patient (33.3%) had nearly response, and 1 patient (33.3%) had moderate response.

Topical retinoids will eliminate reticular and plaquelike as well as erosive OLP. The affected hyperkeratotic mucosa is replaced by an erythematous patch or normal mucosa. However, following withdrawal of the drug, the majority of lesions recur. (3) Topical retinoids may produce burning sensation and irritation if erosive lesions present. (12) Topical applications are usually favored over systemic use, since the latter may be associated with adverse effects such as liver dysfunction, cheilitis and teratogenicity. (3) Additionally, Gorsky and Raviv (67) found the side effects of etritinate including dryness of skin and mucosa; sloughing of skin; skin rash and itching.

Although the use of retinoids in the treatment of OLP seems to show a high success rate, complete remission is difficult to achieve with retinoids alone. Probably, both topical and systemic retinoids should best used as adjuvant therapy or as alternatives when topical steroids fail to be effective. (12)

3. Immunosuppressive agents

The main immunosuppressants used clinically are cyclosporine and azathioprine. (48) Recently, tacrolimus, a macrolide immunosuppressant, has higher activity than that of cyclosporine *in vitro*. (72) Some trials of immunosuppressants in the treatment of OLP are shown in Table VI.

Table VI. Immunosuppressants in the treatment of OLP

Drug	Author	Year	Study type	Pts.* (no.)	Dur. (wks)	Results
I. Topical						
Cyclosporine 100 mg/mL	Frances *et al* (73)	1988	open	4	8	Only one erythematous lesion exists in 3 patients, erosion had disappeared.
	Harpenau *et al* (74)	1995	placebo-controlled	14	4	The lesions had a size reduction of 35.5% when compare with baseline.
	Famiano *et al* (75)	2003	comparative	10	4	All patientss had total clinical resolution of erosions at a mean of 36 days.
Tacrolimus 0.1%	Lener *et al* (76)	2001	case report	1	4	Intra-oral ulcerations resolved after 3 months of daily application.
	Kaliakatsou (72)	2002	open	17	8	There was a 73.3% reduction in the mean surface area of lesions.
	Morrison *et al* (77)	2002	open	6	12	All patients had substantially improvement.
Tacrolimus 0.03%, 0.1%, 0.3%	Rozycki *et al* (78)	2002	retrospective	13	4-16	8 patients had a partial response, 3 patients had complete response and 2 patients had no response.

Pts. = Patients; Dur. = Duration; wks = weeks

* = All patients had erosive OLP.

Table VI. Immunosuppressants in the treatment of OLP (continued)

Drug	Author	Year	Study type	Pts. (no.)	Dur. (wks)	Results
II. Systemic						
Azathioprine 100 mg/d	Lear and English (79)	1996	case reports	2 (s/e)	8	Case 1: Skin lesions were less itchy and flatter (1 month). Erosive OLP had healed after 2 months. Case 2: Skin lesions had almost completely resolved within 1 month. No report of OLP resolution.
Cyclosporine 6 mg/kg/d	Ho *et al* (80)	1990	case reports	2 (s)	8	Both patients had complete remission.

Pts.= Patients; Dur.= Duration; wks.= weeks

s/e = skin lichen planus and erosive OLP; s = skin lichen planus

Several studies have shown that cyclosporine acts selectively on the T-lymphocyte response, and has little or no action on B lymphocytes. Its main use is to prevent graft rejection in organ transplantation. The drug is also used in autoimmune disorders and severe oral ulceration. (48) Although the efficacy of topical cyclosporine in the treatment of OLP has been confirmed in severe studies, but the cost, its hydrophobicity and unpleasant taste are limitations of its use. (3) The oral solution may taste better if mixed with milk or juice by using a glass container. Patients should drink immediately to ensure that the entire cyclosporine dose is swallowed. (62)

Systemic cyclosporine has many adverse effects. It can cause gingival overgrowth as well as phenytoin and calcium-channel blockers. Nephrotoxicity is another well-documented and frequently observed adverse effect. Other adverse effects of cyclosporine include hypertension, hepatotoxicity, neurotoxicity, increased risk of neoplasia, anaemia, and hypertrichosis. (48)

Azathioprine has been widely used as a steroid-sparing agent. (21) The drug is a purine derivative with selective immunosuppressant activity against the cell-mediated system. The use of this drug is also limited due to its adverse effects. The most serious unwanted effect of azathioprine therapy is depression of bone-marrow function causing a leucopenia and thrombocytopenia. (48) Other adverse effects include skin rash, mouth sores, nausea and vomiting, and increased risk of infection. (62)

Topical tacrolimus has recently been approved by the Food and Drug Administration as a safe treatment for atopic dermatitis. (77) The efficacy of topical tacrolimus in the treatment of erosive OLP has been reported on several studies. (72, 76, 77, 78) It has been shown to penetrate the epidermal barrier and exert immunosuppressive actions after topical use. (78) But the long-term risk of use is currently unknown. (77) The adverse effects that have been reported include tingling, and burning sensation, altered taste sensation, slight nausea, mild headache and constipation. (72)

4. Antimicrobials

Despite no evidence for an infectious etiology of OLP, antimicrobial therapies have been administerd. (21) There have been some trials of antimicrobials in the treatment of OLP. (Table VII)

Table VII. Antimicrobials and others in the treatment of OLP

Drug	Author	Year	Study type	Pts. (no.)	Dur. (wks)	Results
Topical tetracycline 250 mg in 100 mL	Walchner *et al* (81)	1999	case report	1 (e)	6	Lesion had totally disappeared and re-epithelization was observed.
Oral tetracycline (Doxycycline) 100 mg/d	Ronbeck *et al* (82)	1990	clinical	6 (DG)	4-11	4 patients had an improvement, 1 no change and 1 worse.
Oral griseofulvin 1000 mg/d	Bagan *et al* (83)	1985	case reports	6 (r/e)	10	None of patients showed signs of improvement.
Oral griseofulvin 500 mg/d	Matthews and Scully (84)	1992	open	11 (b)	12	No obvious clinical changes were observed in all patients.
Dapsone 50 mg/d	Falk *et al* (85)	1985	case report	1 (s/e)	63	Skin lesions had healed. No report of OLP resolution.
Dapsone 50-150 mg/d	Beck and Brandrup (86)	1986	case report	1 (s/e)	49	The lesions on buccal mucosa and toes had completely healed. The erosions on tongue were reduced to 1/4 of pretreatment size.
Dapsone 25-75 mg/d	Matthews *et al* (87)	1989	open	7 (DG)	12	Only 1 patient had complete response. 3 patients experienced no improvement at all. 3 patients showed some gradual improvement.

Pts. = Patients; Dur. = Duration; wks = weeks

e = erosive OLP; DG = desquamative gingivitis; r/e = reticular and erosive OLP,

b = buccal lichen planus; s/e = skin lichen planus and erosive OLP

Table VII. Antimicrobials and others in the treatment of OLP (continued)

Drug	Author	Year	Study type	Pts. (no.)	Dur. (wks)	Results
Hydroxychloroquine 200 to 400 mg/d	Eisen (88)	1993	open	9 (e/a)	24	5 patients had almost complete or complete improvement. 3 patients showed marked improvement and 1 patient improved moderately.
Recomminant interferon alfa-2b 3-10 million IU thrice	Hildebrand *et al* (89)	1995	case reports	3 (s/o)	12	Skin lesions had almost completely resolved. Oral lesions disappeared completely.
Amphotericin 30 mg/d	Lundstrom *et al* (90)	1984	randomized-control	18 (p)	4*	17 patients had improvement. 1 patient with reticular form experienced any change.
Levamisole (Immunostimulants) 150 mg/d	Lu *et al* (91)	1995	prospective follow-up	23 (nr)	288	All patients showed marked improvement with resolution of erosions and ulcers.
Phenytoin (Anticonvulsants) 100-300 mg/d	Bogaert and Sanchez (92)	1990	open	25 (s/o)	6	4 patients with skin and buccal lesions had complete healing. 2 patients with mucosal lesions did not show healing but had great improvement of skin lesions.
Thalidomide (Sedative and antiemetic drug) 150 mg/d	Dereure *et al* (93)	1996	case reports	2 (s/o)		Case 1: Complete healing of distal erosions and an reduction of oral lesions after 4 months of treatment. Case 2: A nearly complete healing in 3 months.

Pts. = Patients; Dur. = Duration; wks. = weeks; * = at least 4 weeks

e/a = erosive and atrophic OLP; s/o = skin lichen planus and OLP, p = positive fungal findings on culture or biopsy; nr = no report type

4.1 Tetracycline

Tetracycline has been shown to have anti-inflammatory properties as well as antibacterial effects. (82) It has been used in treatment of acne, periodontitis, Behcet disease and bullous pemphigoid. (81, 82) Doxycycline monohydrate seems to be the drug of choice because of its good absorption from the gastrointestinal tract, with fewer side effects than related drugs. (82) The use of topical tetracycline hydrochloride seems to be effective for the treatment of erosive OLP, but the side effect is still unknown. (81)

4.2 Griseofulvin

Griseofulvin, an antifungal drug, has no benefit in the treatment of OLP. The mechanism of action of the drug is not known. (83, 84) Moreover, the adverse drug effects include headache, facial pain, nausea, vomiting and diarrhea can be found. (84)

4.3 Dapsone

Dapsone has been used in the treatment of several infectious diseases including leprosy and malaria and recently in the treatment of pneumocystic carinii pneumonia in patients with AIDS. (94) Dapsone has also anti-inflammatory properties and has been used in dermatology and rheumatology. (94) Although dapsone may be useful in severe cases of erosive lichen planus (86), the side effects can develop especially at high dose. They usually include anorexia, nausea, vomiting, headache, tachycardia, nervousness and insomnia. (94) In patients with allergy to sulfa, dapsone should be avoided. In patients with severe cardiac or lung diseases, dapsone doses should be carefully adjusted because of the possible effect on the oxygen transport in cases of hemolysis. Dapsone is contraindicated in patients with deficiency of glucose-6-phosphate dehydrogenase and in patients with severe liver diseases including hepatitis and acute porphyria. Dapsone should be avoided during pregnancy and nursing, if possible. (94)

4.4 Antimalarials

Antimalarial agents including chloroquine, hydroxychloroquine and quinacrine has been well established on the efficacy in the treatment of lupus erythematosus. Moreover, hydroxychloroquine treatment may significantly improve OLP by which the mechanism is unknown. Important adverse effect of hydroxychloroquine is ocular toxicity. It may produce reversible agranulocytosis and idiosyncratic effects including

toxic psychosis, headaches, and neuropathy. Antimicrobial agents have also been implicated as a cause of oral lichenoid eruptions. Thus patients treated with hydroxychloroquine for OLP who have an exacerbation of the disease should have their medication promptly discontinued. (88)

4.5 Interferons

Interferons, cytokines with antiproliferative, antiviral, and immunomodulatory functions, have been used in the treatment of basal cell carcinoma, condylomata acuminata, verruca vulgaris, systemic scleroderma, and chronic granulomatous diseases. Recently, three case reports of generalized lichen planus suggested the beneficial effects of recombinant interferon alfa-2b therapy. However, it cannot be contended with certainty that the observed responses were not the result of spontaneous remission. (89)

4.6 Amphotericin

The treatment of OLP with amphotericin B, an antifungal drug, has also been suggested to be effective. Since yeasts have been found to exist orally in individuals without any clinical symptoms of infection, the possible presence of fungi should be considered. Antifungal agents should be initiated promptly when OLP patients have positive findings. (90)

5. Others

5.1 Immunostimulants (Levamisole)

The combined use of levamisole with prednisolone appeared to be a beneficial modality in the control of severe OLP. Several studies have indicated that levamisole (1) restores normal phagocytic activity of macrophages and neutrophils, (2) immunomodulates or immunopotentiates host defenses (T cell-mediated immunity), (3) potentiates the activity of human interferon and interleukin-2, (4) inhibits fumarate reductase, (5) potently inhibits mammalian alkaline phosphatase, (6) inhibits aerobic tumor glycolysis, and (7) alters the natural course of chronic , recurrent, inflammatory diseases. The use of levamisole with prednisolone might both enhance disease control and facilitate a reduction of the prednisolone treatment dose. However, side effects related to levamisole may develop. They include mild facial skin rash, headache, and insomnia. (91)

5.2 Anticonvulsants (Phenytoin)

Phenytoin also appeared to be of significant benefit in the treatment of generalized lichen planus. It has the ability to promote wound healing, modulate immune function (decrease inflammatory responses), and to act as an antipruritic agent. No side effects of phenytoin were reported in the study. (92)

5.3 Sedative and antiemetic drug (Thalidomide)

Thalidomide has been used in the treatment of several inflammatory mucocutaneous diseases, particularly erythema nodusum, discoid lupus erythamatosus, nodular prurigo, and recurrent giant aphthosis. It acts as an immunomodulatory and anti-inflammatory drug through currently unknown pathways. The use of thalidomide in the treatment of widespread lichen planus appears to be efficacious. The only side effect was a mild lymphopenia, which resolved when treatment was discontinued. (93) Other side effects that have been reported may include headache, nausea, constipation, rash, sedation, erythema nodusum-like lesions, weight gain, and edema. (95)

A number of studies on photochemotherapy, surgery, and enoxaparin in the treatment of OLP are shown in Table VIII.

Table VIII. Photochemotherapy, surgery and enoxaparin in the treatment of OLP

Drug	Author	Year	Study type	Pts. (no.)	Dur. (wks)	Results
Photochemotherapy 16.5 J/cm^2	Lundquist *et al* (96)	1995	comparative randomized	16 (b)	48	9 patients: marked improvement 4 patients: slightly improvement 3 patients: no improvement
Surgical excision	Vedtofte *et al* (97)	1987	open	5 (nr)	-	0% recurrence rate after follow-up period at a mean of 3.88 years.
Cryosurgery	Loitz and Leory (98)	1986	case report	1 (e)	-	Complete remission of symptoms was seen on day 6, the lesion was healed with mild scaring by day 16.
Enoxaparin 3 mg SC once each week	Hodak *et al* (99)	1998	preliminary report	10 (s/o)	4-6	In the 4 OLP patients only 1 showed improvement after 2 months of treatment which was observed concurrent with the improvement of skin lesions. The others showed no improvement.

Pts. = Patients; Dur. = Duration; wks = weeks

b = left or right buccal mucosa, no report type; nr = no report type

e = erosive OLP on tongue; s/o = skin lichen planus and OLP

5.4 Photochemotherapy

Photochemotherapy with psoralens and long-wave ultraviolet light (PUVA) can modulate cellular function of the immune system. PUVA has been reported to be effective in the treatment of cutaneous lichen planus. It also has a therapeutic effect in the treatment of OLP. OLP patients usually received oral methoxsolalen 0.6 mg/kg 2 hours before irradiation. An apparatus of light-cured dental fillings can be used as an irradiation source to deliver a beginning dose of 0.75 J/cm^2. The dose was then increased by 0.25 J/cm^2 every 2 to 3 days. Finally, the patients received a total dosage of 16.5 J/cm^2. The side effects of PUVA including nausea, dizziness, eye-symptoms, numbness, and headache can develop. To avoid systemic side effects, topical trioxsalen ointment associated with perorally administered mathoxsalen has been used. (96)

There is a concern that PUVA therapy has been shown to increase risk of skin cancer. The risk of skin cancer is dose-dependent and a definite risk exists for patients receiving long-term PUVA treatment. The relative risk of cutaneous squamous cell cancer increases significantly after a total cumulative dose of 400 J/cm^2 or after more than 100 treatments. No studies have been done on the relation between oral cancer and PUVA therapy, but it has been reported that the oral mucosa has a greater resistance than skin to PUVA-induced inflammation. Therefore, the risk of oral cancer after PUVA therapy might be less than the risk of skin cancer. The overall risk can be decreased by the use of PUVA treatment in the restricted anatomic site. (96)

5.5 Surgery

5.5.1 Surgical excision

Surgical excision of OLP lesions has been described. The surgical technique was to cover the surgical defect after excision of small to medium sized lesions by direct approximation of the mucosal edges or by transposition of local mucosal flaps. The use of free mucosal transplants was of limited value, mainly due to the size of the needed grafts combined with lack of sufficient amounts of normal mucosa. Free skin grafts were therefore used in the majority of cases for the coverage of larger defects. Skin grafts were frequently used in the floor of mouth and no clinical significant reduction of tongue movement was seen in this technique. (97)

Surgical excision of atrophic and erosive OLP is usually used for the lesions in which recalcitrant to other treatments. (46) Although the lesions have been excised without recurrence (97), the operative trauma to oral mucosa may induce the formation of new lesions. (46) Before surgical treatment, initial biopsy should be performed to confirm clinical diagnosis.

5.5.2 Cryosurgery

Cryosurgery is performed by frozen the lesion with a portable nitrous oxide cryosurgery unit and standard techniques. Recent studies of cryosurgery treatment suggested that freezing can stimulate the immunologic defenses of host, with increases in both IgG and IgM levels. (98) However, cryosurgery may destroy tissue and cause enlargement of the lesion. (46)

5.5.3 Carbondioxide lasers

Carbondioxide lasers have been used to treat erosions with varying rate of recurrence. The procedure causes little discomfort and wounds heal with no contractor or fibrosis. While cryosurgery and carbondioxide lasers may be an adequate treatment for OLP, their use should be limited to carefully selected and previously biopsied lesions as the tissue is destroyed and cannot be examined carefully. (99)

5.6 Enoxaparin

Enoxaparin, a low-molecular-weight heparin, are produced by fractionation of standard heparin; therefore certain batches may contain active disaccharide molecules. Each batch of low-molecular-weight heparin must be tested for immunomodulatory activity. It has been shown to suppress the expression of T-lymphocyte heparinase activity and concurrently inhibit T-cell migration and delayed-type hypersensitivity *in vitro* and *in vivo* studies in animals. (99) Moreover, it was recently shown to inhibit the elicitation of allergic contact dermatitis. This finding led Hodak *et al* (95) to assess the therapeutic effect of enoxaparin in treating lichen planus. It seems to be more effective on cutaneous lichen planus than mucocutaneous lichen planus. (91) No side effects were observed in treating lichen planus. However, it should be aware of direct result of its therapeutic action such as bleeding. (99)

Oral lichenoid lesions

Oral lichenoid lesions (OLL) are seen in about 2% of the adult population. Clinical presentations of OLL include white reticular, erosive or plaque-like pattern. (11) OLL can appear at site atypical for OLP, such as palate and, unlike OLP, lesions tend to be unilateral. (100) Histopathologically, OLL typically shows liquefactive degeneration of the basal layer with a band-like lymphocytic infiltration. (11) The histopathological appearances distinguishing OLL from idiopathic OLP are (1) a subepithelial infiltration containing eosinophils and plasma cells which is more diffuse than in OLP and extends more deeply, (2) a perivascular infiltration, (3) parakeratosis, and (4) the presence of colloid bodies in the epithelium. However, these histological features of OLL can be found in some cases of classic OLP. (101)

The direct immunofluorescence findings in OLL are identical to those in OLP. (101) However, Raghu *et al* (102) have demonstrated a difference in the pattern and intensity of immunofluorescence staining between OLP and OLL. It can be concluded that:

(1) The deposition of fibrinogen at the basement membrane zone was present in both OLP and OLL, but the fluorescence was less intense in OLL.

(2) The pattern of fluorescence was more ragged and fibrillar in OLP, while it was more homogeneous in OLL. (102)

These differences between classic OLP and OLL cannot clearly distinguish OLL from OLP. (10)

Causative agents

Drugs reported as the cause of OLL are shown in Table IX.

Table IX. Drugs implicated in OLL

Drugs	Examples
Antihypertensive agents	ACE inhibitors (Captopril, Enalapril, Ramipril, Quinapril) Beta-blockers (Propanolol, Atenolol) Calcium-channel blockers (Nifedipine, Diltiazem, Isradipine, Diltiazem, Isradipine, Nitredipine) Others (Methyldopa, Hydralazine HCl)
Diuretics	Furosemide, Hydrochlorothiazide
Oral hypoglycemics	Sulphonylureas (Chlopropamide, Tolbutamide, Glibenclamide, Glipizide, Gliclazide)
NSAIDs	Ibuprofen, Naproxen, Phenylbutazone, Diflunisal, Flurbiprofen, Indomethacin
Anti-arthritics (second line)	Penicillamine
Gout preparations	Allopurinol
Psychoactive drugs	Lorazepam, Tricyclic antidepressants (Amitriptyline, Imipramine), Lithium
Anticonvulsants	Carbamazepine
Antipsychotic tranquilizers	Phenothiazines (Chlorpromazine, Fluphenazine, Pericyazine, Perphenazine, Pipothiazine, Prochorperazine, Thioridazine, Trifluoperazine)
Antimalarials	Chloroquine, Quinacrine, Mepacrine, Pyrimethamine, Levamisole, Quinidine, Quinine
Antimicrobial agents	Tetracycline, Ketoconazole, Dapsone, Streptomycin, Penicillin, Para-amino salicylic acid, Sulfonamides
Metals	Bismuth, Gold, Chromium, Mercury
Cough, cold remedies	Triprolidine

The case reports of these drug-induced OLL have been published for many years without confirmed diagnosis. Nevertheless, it is clear that a drug history is essential in evaluation of these patients. (3) It is important to note that some drugs in which are used to treat OLP such as antimalarials, dapsone, and tetracycline have also been implicated as a cause of OLL. (12)

There have been a number of reports suggesting that amalgam fillings may induce OLP or OLL. However, the precise cause relationship is not clear. (103) Wong and Freeman (11) confirmed that OLL can be caused by or associated with allergy to mercury in amalgam fillings. In their study, 86.6% of patients with treatment-resistant OLL with positive patch tests to mercury healed entirely after complete amalgam removal. All patients who responded to replacement of amalgam experienced dramatic resolution of their symptoms within three months. (11) Ido *et al* (104) reported an OLP case with a positive patch test to zinc. The lesions subsided three months after the removal of metal restorations. (104)

Pemberton *et al* (105) reported a case in which OLL developed after vaccination against hepatitis B. The patient was received the Engerix B vaccine. Approximately three weeks after the third injection, acute soreness and ulceration of buccal mucosae and tongue developed. It is possible that OLL is due to one of the vaccine constituents other than the protein S in the vaccine. (105)

Diagnostic criteria

There is currently no specific test to identify OLL. (101, 102) The differentiation between OLL and OLP is based only on the association of OLL with a drug or amalgam fillings and its resolution when the causative agent is removed. (3) Therefore, a history of current use of a known OLL inducing drug; a typical oral lesions associated with amalgam fillings; and a histopathological appearance consistent with OLL must be combined to make a diagnosis of OLL. (101)

Management

Since OLL can be a painful and recalcitrant condition, the persuit of a treatable cause is clearly important. (11) Drug substitution or withdrawal should be done by consulting physicians in patients with drug induced OLL. The majority of drug-induced OLL resolves promptly when the offending drug is eliminated. (3) In patients receiving potent OLL-inducing agents such as gold, penicillamine and methyldopa,

symptoms can persist for long periods following drug withdrawal. (100) Therefore, the effective medication may be required for symptomatic relief in these patients.

Removal of amalgam fillings should be recommended in all symptomatic OLL patients associated with restorations. Some authors found a significantly better response to amalgam removal in patients with positive tests to mercury. (106) However, in the study of Dunshe *et al* (106), the response to amalgam removal of lesions in patients with sensitization to mercury did not differ from those with negative patch tests. Nevertheless, patients with positive patch tests to amalgam showed complete healing more frequently than the negative group. (106) Furthermore, in patients who had lesions in direct contact with amalgam, there was a better response than in patients with lesions exceeded the contact area or without contact to amalgam. (11, 106) It is possible that, amalgam fillings in which direct contact with oral mucosa may directly alter the antigenicity of basal keratinocytes by the release of mercury and other metal salts as corrosion products. In susceptible individuals, amalgam fillings may induce OLL that are likely to occur on mucosal surfaces in intimate contact with amalgam fillings. (103)

A positive patch test with amalgam or mercury can indicate a better effect of amalgam removal for some patients, but the predictive value of patch tests with amalgam and mercury appears to be very limited in most cases. Nevertheless, a patch test with common dental materials is mandatory in order to exclude a pre-existing contact allergy to the new filling materials. (106)

Not only amalgam fillings in direct contact with the mucosa needed to be removed to achieve lesion resolution, but also replacement of other fillings or crown restorations associated with lesions. However, it became clear that inert materials such as composite resin, glass ionomer are preferable. (103) Like drug-induced OLL, medication for lesions associated with restorations may be required to relieve symptoms.

Regarding to malignant transformation of OLL, it has not been investigated. Despite few of the support evidences, it dose not preclude the possibility of its malignant transformation. (101)

Centella asiatica

Centella asiatica is the most ubiquitous species of Centella. It is found in Southeast Asia, Sri Lanka, in parts of China, in the western South Sea Islands, Madagascar, South Africa, in the southeast of the U.S.A., Mexico, Venezuela and Columbia, as also in the eastern regions of South America. (14)

The substances of therapeutic interest are the saponin-containing triterpene acids and their sugar esters. The important components in these substances are asiatic acid, madecassic acid and the three asiaticosides, asiaticoside, asiaticoside A and asiaticoside B. (14)

The Centella preparations used in conventional medicine are employed in oral form (tablets and drops), topically (ointments and powders) and in the form of injections (SC, IM, IV). (14)

Pharmacological profile of *Centella asiatica*

1. Pharmacokinetics

In animal experiments, an *in vivo* transformation of asiaticoside into asiatic acid was established. It was demonstrated that the maximum plasma concentration of asiatic acid increased significantly with increasing dose administered, while the time point of maximum plasma concentration and the elimination half-life did not significantly change with increasing dose. (14)

In comparison with a single oral administration, repeated oral dose have been sound to significantly increase the maximum plasma concentration and the elimination half-life. (14)

A comparison of figures measured after oral and subcutaneous administration of madecassoside, asiaticoside, asiatic acid and madecassic acid in rats revealed a bio-availability varying between 30% and 50%. (107)

2. Pharmacodynamics

The pharmacodynamie effects of *Centella asiatica* have been investigated in numerous animal experiments and *in vitro* studies. Demonstrated actions include an anti-inflammatory, a wound healing, ulcer-protective, psychoneuro-pharmacological, antimicrobial and antiviral effect of the Centella or asiaticoside extract. (14)

1. Anti-inflammatory effect

The finding of anti-inflammatory activity of the aerial parts of *Centella asiatica* when administered orally was documented in a study carried out among chronic arthritis patients. (108)

2. Wound healing acceleration

Shukla *et al* (109) indicated that wound areas of normal animals in 0.2% asiaticoside treated wounds decreased by 56% and 54% on seventh and tenth day post wounding, respectively, as compared to vehicle treated controls of the same day. Lower concentration (0.05% and 0.1%) were found to have no significant effect on wound area. Moreover, the topical application of 0.4% asiaticoside solution to wound of diabetic animals produced 42% reduction in wound areas as compared to vehicle treated diabetic controls.

The application of titrated extract of *Centella asiatica* (a defined mixture of asiaticoside 40% w/w, asiatic acid 30% w/w, and madecassoside 30% w/w) to human fibroblast cells has previously been shown to increase collagen synthesis in a dose dependent fashion. (110)

Moreover, titrated extract of *Centella asiatica* has been shown to drive changes in hyaladherin and cytokine expression which may be expected to lower the rate of proteolysis in the extracellular matrix, and thereby support the accumulation of collagen and fibronectin. (111)

3. Ulcer-protective and anti-ulcer effects

Ravokatra *et al* (112) induced gastrointestinal ulcers in mice and investigated the ulcer-protective effect of asiaticoside administered subcutaneously three hours prior to exposure to cold. The formation of ulcers was significantly reduced by the asiaticoside. The post-traumatic oral administration of asiaticosides resulted in a significant reduction in the number of ulcers induced by mercapto-ethylamine. Furthermore, their study showed accelerated healing of the induced lesions.

4. Psychoneuro-pharmacological profile

Sakina and Dandiya (113) investigated the psychoneuro-pharmacological effects of an orally administered alcoholic extract of *Centella asiatica* in rats and mice. A significant prolongation of sleeping time in mice treated with phenobarbitone was observed.

Diwan *et al* (114) investigated the psychoneuro-pharmacological properties of an aqueous extract of *Centella asiatica* in mice. The Centella extract reduced spontaneous motor activity in the mice to the same extent as did the reference substance diazepam.

5. Antimicrobial and antiviral effects

In the available pharmacological studies, an antibacterial effect against *Pseudomonas pyocyaneus*, *Trichoderma mentagrophytes* and *Entamoeba histolytica* has been demonstrated. Both the alcoholic and the aqueous extract of *Centella asiatica* developed an antiviral action against herpes simplex virus. (14)

6. Immunomodulatory effects

The effect of an aqueous extract of Centella on the human complement system was the subject of a pharmacodynamics *in vitro* study carried out by Labadie *et al* (115). A positive effect of the Centella extract on both the classical and the alternative pathway of complement activation were demonstrated.

7. Spasmolytic effects

Dhar *et al* (116) investigated, *in vitro*, the spasmolytic effects of an alcoholic extract of *Centella asiatica* on isolated ileum tissue obtained from pigs. After contact with isolated ileum tissue, the Centella extract developed a spasmolytic effect.

8. Effects on varicose veins

Arpaia *et al* (117) investigated the biochemical action of an extract of *Centella asiatica* administered three times daily in 20 patients with severe varicose veins in the leg over an observation period of three months. Following treatment, there was a significant reduction in the serum levels of uric acid and the lysosomal enzymes. This reduction is interpreted as evidence of a positive effect of Centella extract on varicose veins.

Complementary medical application

Centella asiatica is used for homeostatic applications. In this field, *Centella asiatica* is employed mainly in the treatment of skin lesions. The homeopathic spectrum of indications includes the initial treatment of psoriasis and pruritic skin lesions. (14)

Adverse reactions

Adverse reactions following the use of *Centella asiatica* have repeatedly been described. Allergic contact dermatitis has been reported after the topical application of

various creams and ointments. Following oral administration of Centella preparations, gastric complaints and nausea have occasionally been reported, but were not significant versus placebo. (14)

CHAPTER III
PATIENTS AND METHODS

Forty-two patients with atrophic and/or erosive OLP or OLL attending the Oral Medicine Clinic, Faculty of Dentistry, Mahidol University, volunteered in the study. All patients received information on the study and signed in the informed consent form. They were interviewed for a thorough history including chief complaint, present illness, past medical history, personal history, allergy, current medications, family history, social and dental history. Patients with cutaneous lichen planus, pregnancy and lactation were excluded from the study. Diagnosis of OLP and OLL were made by history and clinical examination. Biopsy was performed to confirm clinical diagnosis by histopathologic examination and direct immunofluorescence. The patients' lesions were not treated with any topical medications for at least two weeks before the study. (54) Moreover, any systemic medications for OLP and OLL treatments were stopped for at least one month before the study. Candidal cultures with swab technique were completed on all patients to rule out secondary candidal infection. (29)

Drugs

1. Triamcinolone acetonine in orabase 0.1% (Oral-T Oral paste) supplied by Silom Medical Co.Ltd.
2. *Centella asiatica* in orabase was a crude extract of *Centella asiatica* mixed in an orabase. It was prepared by the Faculty of Pharmacology, Mahidol University.
3. Placebo was an orabase prepared by the Faculty of Pharmacology, Mahidol University.

Study design

All patients received instructions on nature of the disease, exacerbating factors, goals of treatment, follow-up and oral hygiene control. The prophylaxis and elimination of irritating factors were performed. The patients with positive candidal

culture were treated with topical antifungals for one month before the beginning of study.

Patients were ranked according to the severity of their lesions. On this basis, the patients were then evenly distributed into three groups. The three groups were given triamcinolone acetonide in orabase 0.1%, *Centella asiatica* in orabase or placebo, respectively. Patients receiving triamcinolone acetonide in orabase 0.1%, *Centella asiatica* in orabase, and placebo were the study group A, B, and C, respectively. There were fourteen patients in each group.

The patients were instructed to apply the medication on dried lesions four times a day, after three meals and before bedtime. Before application, toothbrushing or mouthwash with plain water was recommended. After application, mouthrinsing, drinking and eating were restrained for 30 minutes. Moreover, they were requested not to use any systemic medication and other topical agents to treat the lesions during the study. The most severe lesions in each individuals were evaluated in this study. At the beginning, the severity of lesions and pain in each patient were assessed.

The severity of OLP and OLL was assessed by scoring. Severity score ranged from 0 (no lesion) to 5 (most severe lesion). The criteria for scoring was as follows (54):

Score 5 = white striae with erosive area more than 1 cm^2

Score 4 = white striae with erosive area less than 1 cm^2

Score 3 = white striae with atrophic area more than 1 cm^2

Score 2 = white striae with atrophic area less than 1 cm^2

Score 1 = mild white striae, no erythematous area

Score 0 = no lesion, normal mucosa

The visual analogue scale was used for pain assessment. (29) Patients were asked to score their intensity of pain on a 10-cm visual analogue scale. Pain scores ranged from 0 (no pain) to 10 (worst pain imaginable). (118)

The severity of lesions and pain in patients were assessed at second week and fourth week of study. During the study, the patients'compliances were evaluated. Moreover, secondary candidiasis was also observed. At the end of study, patients that still had lesions and symptoms were treated with conventional therapy.

This study design was approved by the Committee on Human Rights Related to Human Experimentation, Mahidol University on 6 November, 2003 (No. 187/2003).

Statistical analysis

Data of severity scores and pain scores from the three study groups were analyzed as follows:

1. The severity scores before and after treatment in each study group were analyzed by Wilcoxon Signed Rank test.
2. The severity scores of the three study groups after treatment were compared by Kruskal Willis k-sample test.
3. The pain scores before and after treatment in each study group were analyzed by Paired t-test.
4. The pain scores of the three study groups after treatment were compared by One way analysis of variance.

CHAPTER IV
RESULTS

A total of forty-two patients with atrophic and/or erosive OLP or OLL were assessed in the study groups A, B, and C. The study groups A, B, and C were patients receiving triamcinolone acetonide in orabase 0.1%, *Centella asiatica* in orabase, and placebo, respectively.

Number of patients according to previous treatments and candidal culture at the beginning are shown in Table X. The number of patients that had been received the treatment of OLP and OLL was approximate to number of patients that had never been received the treatment of OLP and OLL. The number of patients with positive culture to *Candida* was lower than that with negative culture to *Candida*. Factors that might be related to candidiasis in each individual are shown in Table XI. Topical antifungals were given to these patients for one month before beginning of the study.

Sex and type of diseases in patients of the three study groups are shown in Table XII. Women were the majority in every group. OLP was more common than OLL in each group.

Mean age of patients and mean duration of diseases in patients of the three study groups are shown in Table XIII. Of all the patients, the mean age was 53.2 years. The mean duration of disease was one year and eight months.

Number of patients according to type and location of lesions in the three study groups are shown in Table XIV. The number of atrophic lesions was higher than that of erosive lesions in all three study groups. Lesions of patients in group A, B, and C were mostly found at the buccal mucosa and gingiva, at the gingiva, and at the buccal mucosa, respectively.

The most severe lesion in each patient was assessed. The severity scores of the lesions were recorded at the beginning, second week, and fourth week of treatment. Pain scores were also assessed at the same period. Changes in the severity scores were

calculated from scores at the beginning minus scores at the end of treatment. Thus, the negative results showed improvement of the lesion severity. The zero results indicated no change of the lesion severity. The positive results implied that the lesions got worse. Changes in the pain scores after treatment were determined as decrease, no change, or increase from scores at the beginning.

The locations of lesions, severity scores, and changes in severity scores of patients in the three study groups are shown in Table XV (A-C).

In patients receiving triamcinolone acetonide in orabase 0.1%, the lesions were mostly at the buccal mucosa, followed by gingiva and mucobuccal fold, respectively. The lesions at the beginning of treatment were mostly atrophic lesions more than 1 cm^2. Most lesions at the second and fourth week of treatment improved to atrophic lesion less than 1 cm^2 as shown in Figure 2 and 3. Only one OLP lesion cured (score 1). The changes in severity scores were mostly negative, indicating improvement of lesions. Three lesions did not change in their severity.

In patients receiving *Centella asiatica* in orabase, the lesions were mostly at the buccal mucosa, followed by mucobuccal fold and gingiva, respectively. The lesions at the beginning of treatment were mostly atrophic lesions less than 1 cm^2. At the second and fourth week of treatment, most lesions had no change but decreased in erythema as shown in Figure 4. Two OLP lesions improved in their severity as shown in Figure 5.

In patients receiving placebo, the lesions were mostly at the buccal mucosa, followed by mucobuccal fold, gingiva, and tongue, respectively. The lesions at the beginning of treatment were mostly atrophic lesions more than 1 cm^2. At the second and fourth week of treatment, most lesions had no change as shown in Figure 6. One OLP lesion got worse as shown in Figure 7.

The summary of changes in severity scores after four weeks of treatment in the three study groups are shown in Table XVI. Eleven patients (78.6%) receiving triamcinolone acetonide in orabase 0.1% had improvement of their lesions. No improvement of lesions in three patients (21.4%) receiving triamcinolone acetonide in orabase 0.1%. Two patients (14.3%) receiving *Centella asiatica* in orabase had improvement in their lesions. No improvement of lesions in twelve patients (85.7%) receiving *Centella asiatica* in orabase. There was no improvement of lesions in

thirteen patients (92.9%) receiving placebo. The other one (7.1%) had deteriorated lesion.

At the beginning of treatment, the mean average severity scores of lesions were 2.9, 2.8, and 2.8 in patients receiving triamcinolone acetonide in orabase 0.1%, *Centella asiatica* in orabase, and placebo, respectively. When severity scores were analyzed by Kruskal-Wallis k-sample test, no statistically significant difference in the severity score at the beginning of treatment was found within the three study groups ($p = 0.824$). At the end of treatment, the mean average severity scores of lesions were 1.9, 2.6, and 2.9 in patients receiving triamcinolone acetonide in orabase 0.1%, *Centella asiatica* in orabase, and placebo, respectively. The severity scores before and after treatment in each groups were analyzed by Wilcoxon Signed Rank test. There was a statistically significant difference in the severity scores before and after treatment in patients receiving triamcinolone acetonide in orabase 0.1%. ($p < 0.001$). Whereas, no statistically significant difference in the severity scores before and after treatment was found in patients receiving *Centella asiatica* in orabase and placebo ($p = 0.5$ and $p = 1$, respectively).

The severity scores of the three study groups after treatment were analyzed by Kruskal-Wallis k-sample test. The severity scores in patients receiving triamcinolone acetonide in orabase 0.1% was statistically significant lower than that in patients receiving *Centella asiatica* in orabase and placebo ($p < 0.05$). No statistically significant difference in the severity scores was observed between patients receiving *Centella asiatica* in orabase and placebo ($p > 0.05$ and $p > 0.05$, respectively).

The changes in pain scores in the three study groups during and at the end of treatment are shown in Table XVII. The number of patients with pain decrease was higher in patients receiving triamcinolone acetonide in orabase 0.1% than that of patients receiving *Centella asiatica* in orabase and placebo after two and four weeks of treatment.

The mean pain score with standard deviation of patients in the three study groups are presented in Figure 8 and 9. The mean pain scores were gradually decreased from the beginning to the end of treatment in all study groups. (Figure 8)

When pain scores at the beginning and the end of treatment in each group were analyzed by Paired t-test, there was a statistically significant difference in the pain

scores of patients receiving triamcinolone acetonide in orabase 0.1%, *Centella asiatica* in orabase, and placebo ($p < 0.001$, $p < 0.001$, and $p = 0.002$, respectively). Figure 9 shows mean score of three study groups at the beginning, 2 weeks and 4 weeks after treatment. When pain scores of the three study groups were compared by One way analysis of variance , no statistically significant difference in the pain scores was observed ($p = 0.134$).

About 29% of patients receiving *Centella asiatica* in orabase complained of its sticky. At the end of treatment, eleven patients (78.6%) did not favor to further apply *Centella asiatica* in orabase.

No side effects were noticed in all study groups. In the triamcinolone acetonide in orabase 0.1% group, one OLP patient with negative candidal culture at the beginning developed acute pseudomembranous candidiasis at the fourth week of treatment.

Table X. Number of patients according to previous treatments and candidal culture

Group	No. of patients	No. of patients			
		Previous treatments		Candidal culture	
		No	Yes	Negative	Positive
A	14	8 (57.1%)	6 (42.9%)	11 (78.6%)	3 (21.4%)
B	14	6 (42.9%)	8 (57.1%)	11 (78.6%)	3 (21.4%)
C	14	8 (57.1%)	6 (42.9%)	9 (64.3%)	5 (35.7%)
Total	42 (100)	22 (52.4%)	20 (47.6%)	31 (73.8%)	11 (26.2%)

Group A: Patients receiving triamcinolone acetonide in orabase 0.1%

Group B: Patients receiving *Centella asiatica* in orabase

Group C: Patients receiving placebo

Table XI. Factors that might be related to candidiasis in each individuals

Factors	No. of patients
Removable dentures	3
Application of topical corticosteroids	3
Oral hypoglycemic and antihypertensive drugs	1
Antihypertensive drug	2
Old age	1
Unknown	1

Table XII. Sex and type of diseases in the patients of three study groups

Group	No. of patients	Sexes (%)		Type of diseases (%)	
		Women	Men	OLP	OLL
A	14	12 (28.6)	2 (4.8)	12 (28.6)	2 (4.8)
B	14	11 (26.2)	3 (7.1)	13 (30.9)	1 (2.4)
C	14	13 (30.9)	1 (2.4)	12 (28.6)	2 (4.8)
Total	42 (100)	36 (85.7)	6 (14.3)	37 (88)	5 (12)

Group A: Patients receiving triamcinolone acetonide in orabase 0.1%

Group B: Patients receiving *Centella asiatica* in orabase

Group C: Patients receiving placebo

Table XIII. Mean age of patients and mean duration of diseases in patients of the three study groups

Group	No. of patients	Mean age (Years)	Mean duration (Months)
A	14	51.9 (36-71)	20.1 (1-132)
B	14	54.7 (18-71)	19.7 (2-132)
C	14	53.1 (32-78)	20.2 (1-132)
Total	42 (100)	53.2 (18-78)	20 (1-132)

Group A: Patients receiving triamcinolone acetonide in orabase 0.1%

Group B: Patients receiving *Centella asiatica* in orabase

Group C: Patients receiving placebo

Table XIV. Number of patients according to type and location of lesions in the three study groups

	No. of patients						
	No. of	Type of lesions (%)		Location of lesions (%)			
Group	patients	E	A	B	G	T	M
A	14	3 (7.1)	11 (26.2)	9 (21.4)	9 (21.4)	1 (2.4)	3 (7.1)
B	14	3 (7.1)	11 (26.2)	9 (21.4)	10 (23.8)	0 (0)	6 (14.3)
C	14	2 (4.8)	12 (28.6)	11 (26.2)	7 (16.7)	2 (4.8)	9 (21.4)
Total	42 (100)	8 (19)	34 (81)	29 (69)	26 (61.9)	3 (7.1)	18 (42.9)

Group A: Patients receiving triamcinolone acetonide in orabase 0.1%

Group B: Patients receiving *Centella asiatica* in orabase

Group C: Patients receiving placebo

E: Erosive lesion; A: Atrophic lesion;

B: Buccal mucosa; G: Gingiva; T: Tongue; M: Mucobuccal fold

Table XV (A). Locations of lesions, severity scores and change in severity scores in patients receiving triamcinolone acetonide in orabase 0.1%

Patient No.	Lesion	Severity scores			Change in severity scores (end-beginning)
		Beginning	Second week	Fourth week	
1	B	3	2	2	-1
2	B	3	2	2	-1
3	B	3	2	2	-1
4	G	3	2	2	-1
5	B	4	2	2	-2
6	G	4	2	2	-2
7	G	3	2	2	-1
8	G	2	1	1	-1
9	G	4	2	2	-2
10	B	3	2	2	-1
11	B	2	2	2	0
12	B	3	2	2	-1
13	M	2	2	2	0
14	B	2	2	2	0

Beginning: Severity scores at the beginning of treatment

Second week: Severity scores at the second week of treatment

Fourth week: Severity scores at the fourth week of treatment

end-beginning: Severity scores at the end of treatment minus severity scores at the beginning of treatment

B: Buccal mucosa; G: Gingiva; M: Mucobuccal fold

Table XV (B). Locations of lesions, severity scores and change in severity scores in patients receiving *Centella asiatica* in orabase

Patient No.	Lesion	Severity scores			Change in severity scores (end-beginning)
		Beginning	Second week	Fourth week	
1	B	4	3	3	-1
2	G	2	2	2	0
3	M	3	3	3	0
4	B	3	3	3	0
5	B	3	3	3	0
6	M	4	2	2	-2
7	B	3	3	3	0
8	M	2	2	2	0
9	G	4	4	4	0
10	B	2	2	2	0
11	B	2	2	2	0
12	M	2	2	2	0
13	B	2	2	2	0
14	B	3	3	3	0

Beginning: Severity scores at the beginning of treatment

Second week: Severity scores at the second week of treatment

Fourth week: Severity scores at the fourth week of treatment

end-beginning: Severity scores at the end of treatment minus severity scores at the beginning of treatment

B: Buccal mucosa; G: Gingiva; M: Mucobuccal fold

Table XV (C). Locations of lesions, severity scores and change in severity scores in patients receiving placebo

Patient No.	Lesion	Severity score			Change in severity scores (end-beginning)
		Beginning	Second week	Fourth week	
1	T	2	2	2	0
2	M	4	4	4	0
3	M	2	2	2	0
4	B	4	4	4	0
5	B	2	2	2	0
6	G	3	3	3	0
7	M	2	2	2	0
8	G	2	2	2	0
9	M	3	3	3	0
10	B	3	3	4	1
11	B	3	3	3	0
12	M	3	3	3	0
13	B	3	3	3	0
14	M	3	3	3	0

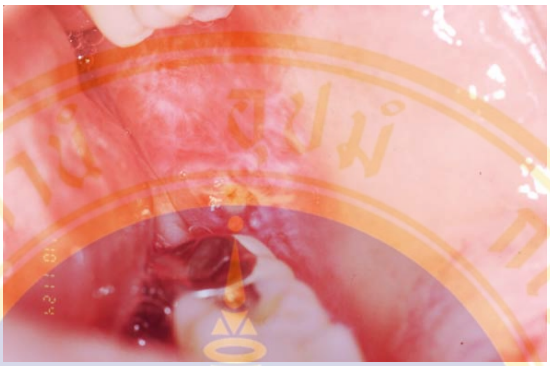
Beginning: Severity scores at the beginning of treatment

Second week: Severity scores at the second week of treatment

Fourth week: Severity scores at the fourth week of treatment

end-beginning: Severity scores at the end of treatment minus severity scores at the beginning of treatment

B: Buccal mucosa; G: Gingiva; T: Tongue: M: Mucobuccal fold



(a)

(b)

Figure 2. (a): An OLP lesion on left buccal mucosa before treatment with triamcinolone acetonide in orabase 0.1%,

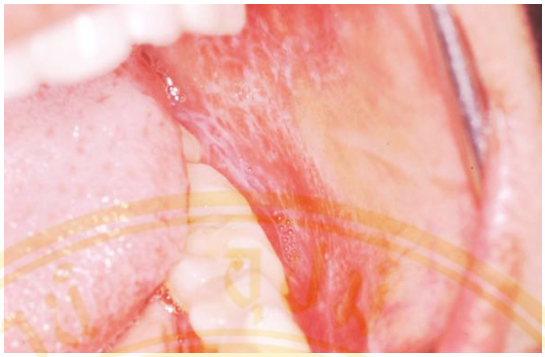
(b): The same OLP lesion after four weeks of treatment with triamcinolone acetonide in orabase 0.1%

(a)

(b)

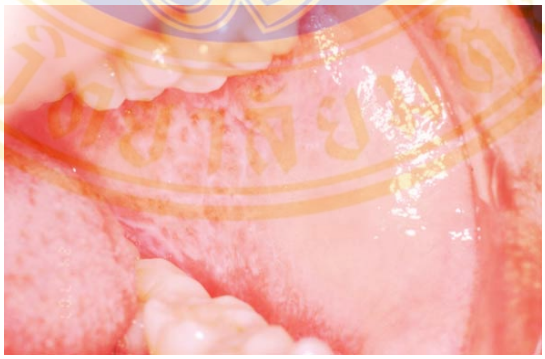
Figure 3. (a): An OLL lesion on right buccal mucosa before treatment with triamcinolone acetonide in orabase 0.1%,

(b): The same OLL lesion after four weeks of treatment with triamcinolone acetonide in orabase 0.1%



(a)

(b)

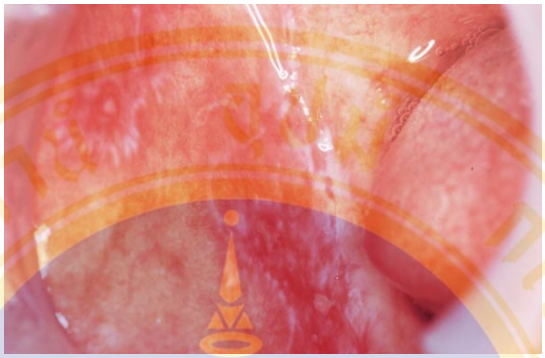


(c)

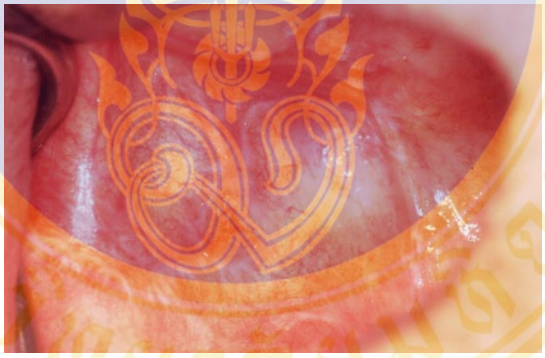
Figure 4. (a): An OLP lesion on left buccal mucosa before treatment with *Centella asiatica* in orabase,

(b): The same OLP lesion after two weeks of treatment with *Centella asiatica* in orabase,

(c): The same OLP lesion after four weeks of treatment with *Centella asiatica* in orabase



(a)



(b)

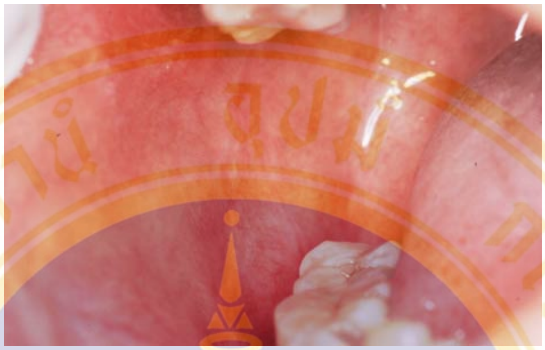
Figure 5. (a): An OLP lesion on right buccal mucosa before treatment with *Centella asiatica* in orabase,

(b): The same OLP lesion after four weeks of treatment with *Centella asiatica* in orabase

(a)

(b)

Figure 6. (a): An OLP lesion on gingiva before treatment with placebo,
(b): The same OLP lesion after four weeks of treatment with placebo



(a)

(b)

Figure 7. (a): An OLP lesion on right buccal mucosa before treatment with placebo, (b): The same OLP lesion after four weeks of treatment with placebo, ulcers developed.

Table XVI. Changes in severity scores after four weeks of treatment in the study groups

	Number of patients (%) Changes in severity scores (At the end-at the beginning)				
Group	-2	-1	0	1	Total
A	3 (21.4%)	8 (57.1%)	3 (21.4%)	0 (0%)	14 (100%)
B	1 (7.1%)	1 (7.1%)	12 (85.7%)	0 (0%)	14 (100%)
C	0 (0%)	0 (0%)	13 (92.9%)	1 (7.1%)	14 (100%)

Group A: Patients receiving triamcinolone acetonide in orabase 0.1%

Group B: Patients receiving *Centella asiatica* in orabase

Group C: Patients receiving placebo

Table XVII. Changes in pain scores in the three study groups after two and four weeks of treatment

	Number of patients (%)					
	Pain scores after 2 weeks			Pain scores after 4 weeks		
Group	Decrease	No change	Increase	Decrease	No change	Increase
A	13 (92.8)	1 (7.1)	0 (0)	13 (92.8)	1 (7.1)	0 (0)
B	10 (71.4)	3 (21.4)	1 (7.1)	11 (78.6)	1 (7.1)	2 (14.3)
C	11 (78.6)	2 (14.3)	1 (7.1)	10 (71.4)	3 (21.4)	1 (7.1)

Group A: Patients receiving triamcinolone acetonide in orabase 0.1%

Group B: Patients receiving *Centella asiatica* in orabase

Group C: Patients receiving placebo

Decrease: Pain score at the end decrease when compared with pain score at the beginning

No change: Pain score at the end are the same as pain score at the beginning

Increase: Pain score at the end increase when compared with pain score at the beginning

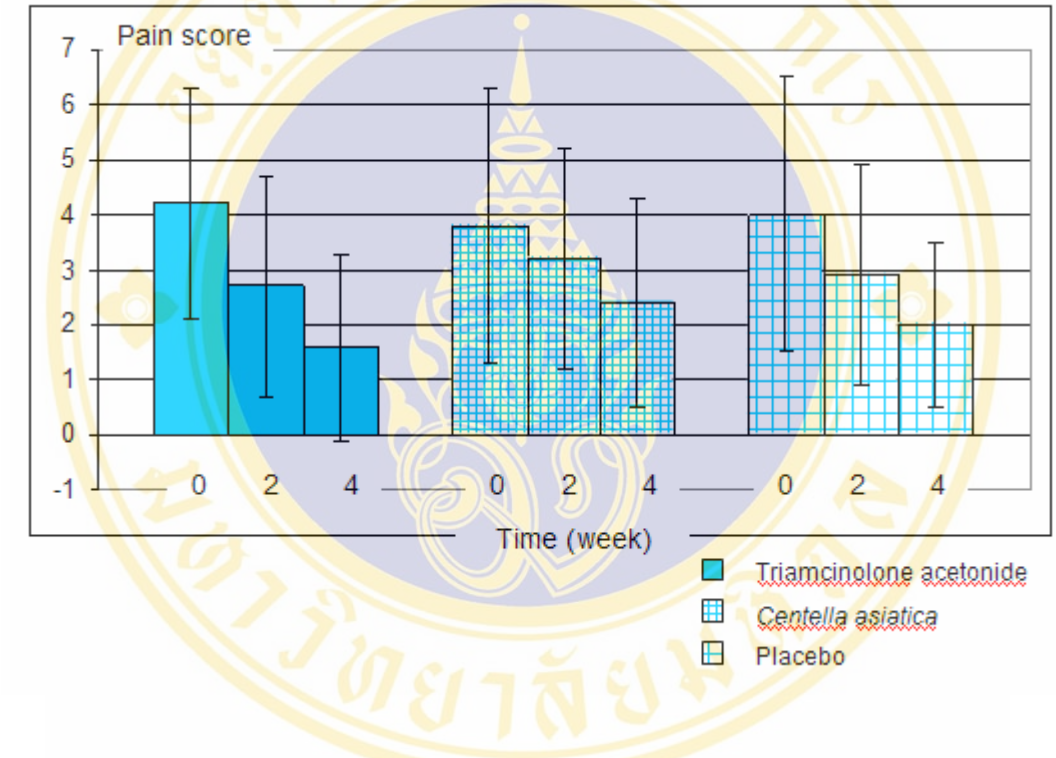


Figure 8. Mean pain score with standard deviation of three study groups at the beginning of treatment (week 0), after two weeks (week 2) and four weeks (week 4) of treatment

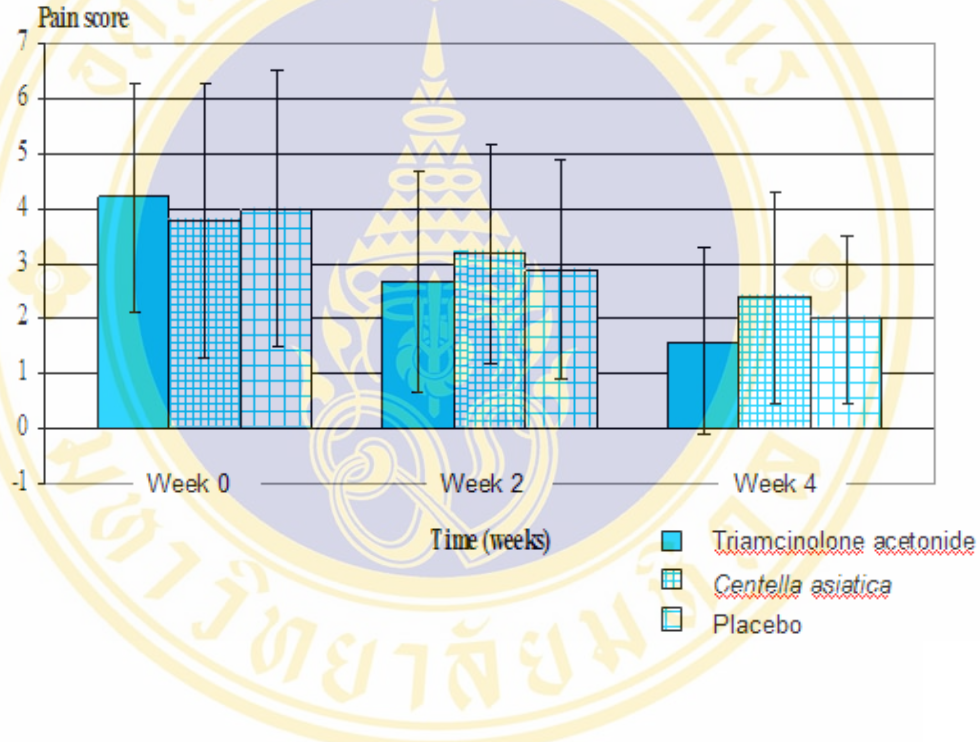


Figure 9. Mean pain score with standard deviation of three study groups at the beginning of treatment (week 0), after two weeks (week 2) and four weeks (week 4) of treatment

CHAPTER V
DISCUSSION

The mainstay of OLP and OLL treatment has been the administration of topical corticosteroids. (29) Triamcinolone acetonide in orabase 0.1% is commonly prescribed. (2) The other medications such as retinoids, immunosuppressants, antimicrobials have been used to treat OLP and OLL, however, their uses are limited by their side effects. (12)

Centella asiatica was found to have an anti-inflammatory activity when administered orally in patients with chronic arthritis. (108) The Faculty of pharmacology, Mahidol University has developed *Centella asiatica* in orabase for the treatment of oral lesions. If it can reduce severity of lesions and relieve pain in patients with oral diseases without serious effects, it would be an alternative agent in the treatment of these diseases.

This study compared the efficacy of *Centella asiatica* in orabase with triamcinolone acetonide in orabase 0.1% and placebo in the treatment of OLP and OLL. The patients in this study were atrophic and/or erosive OLP and OLL patients. These diseases are commonly seen in patients referred to the Oral Medicine Clinic. The patients were orderly allocated by their lesion severity to give triamcinolone acetonide in orabase 0.1%, *Centella asiatica* in orabase, or placebo.

In patients used triamcinolone acetonide in orabase 0.1%, the improvement of severity scores was observed in 11 of 14 patients (78.6%) after four weeks of treatment. Of these, the lesion in only one patients (7.2%) was cured. The cure percentage in this study is lower than that in the study of Thongprasom *et al* (54) In their study, the lesions in 8 of 19 patients (42.1%) with erosive and atrophic OLP were cured after four weeks of treatment with triamcinolone acetonide in orabase 0.1%. There were differences in the mean age and location of lesions between both studies. Generally, gingival lesions are recalcitrant to treatment as they may increase in

severity from secondary periodontal infection. (21) Gingival lesions were found in 21.4% of patients in this study.

In patients using *Centella asiatica* in orabase, the improvement of lesions was observed in 2 of 14 patients (14.3%) after four weeks of treatment. Although most lesions had no change in their severity, the decrease in erythema was noticed. As the treatment of OLP and OLL lesions with large size and/or ulcer may require high-potency corticosteroids, the use of *Centella asiatica* in orabase may not be appropriate in these cases.

In patients using placebo, no improvement of lesions was observed in each individuals. Moreover, one OLP patient with atrophic lesion on buccal mucosa developed an ulcer during the treatment. Because placebo was an orabase without anti-inflammatory agent, the use of placebo could not control the disease in exacerbation period.

Positive cultures to *Candida* were found in 11 of 42 patients (26.2%) before the beginning of study. These patients had predisposing factors including old age and the usage of prostheses, topical corticosteroids, and drugs with xerostomic side effects. (31)

Only one patient taking antihypertensive drug with negative culture before the beginning developed acute pseudomembranous candidiasis at the fourth week of treatment with triamcinolone acetonide in orabase 0.1%. This might be due to overdose of medication and/or xerostomic side effect of antihypertensive drug. In the studies of Thongprasom *et al* (54) and Rodstrom *et al* (51), they did not observe secondary candidiasis in patients using triamcinolone acetonide in orabase 0.1% but in patients using fluocinolione acetonide in orabase 0.1% (54) and clobetasol proprionate in orabase 0.05% (51). This might be related to lymphocytic suppression in high-potency corticosteroids. (48)

Although pain is a subjective and private event, pain assessment can accomplish in individuals. (118) Previous studies have been indicated that VAS is the most sensitive and reliable of pain assessment in humans. (118) Moreover, the use of VAS is an easy method to administration and scoring. (118) The visual analogue scale (VAS) was used for the pain assessment in this study.

The decrease in pain scores was found in most patients using triamcinolone acetonide in orabase 0.1%, *Centella asiatica* in orabase, and placebo. The severity of lesions did not seem to be related to pain scores. The protective effect of medications might play a role in pain decrease found in all study groups.

Centella asiatica in orabase showed some anti-inflammatory effects as some lesions had an improvement. But the potency of anti-inflammation of *Centella asiatica* in orabase is lower than that of triamcinolone acetonide in orabase 0.1%. The concentration of crude extract of *Centella asiatica* in orabase may need to be increased. The development in preparation of medication may be required for increasing favor in patients. Further studies on the efficacy of *Centella asiatica* in orabase in other oral diseases should be performed.

CHAPTER VI
CONCLUSION

This study compared the efficacy of *Centella asiatica* in orabase with triamcinolone acetonide in orabase 0.1% and placebo in the treatment of OLP and OLL. The severity of lesions and pain in patients were assessed.

The results from this study showed that:

1. The severity scores after four-week treatment in patients receiving triamcinolone acetonide in orabase 0.1% were statistically significant lower than those in patients receiving *Centella asiatica* in orabase or placebo. There were no statistically significant differences in the severity scores of patients receiving *Centella asiatica* in orabase and placebo at the end of treatment.
2. The pain scores after four-week treatment were statistically significant decreased in patients receiving triamcinolone acetonide in orabase 0.1%, *Centella asiatica* in orabase or placebo. There were no statistically significant differences in the pain scores of the three treatment groups at the end of study.

Therefore, the lesion severity was significantly improved in patients receiving triamcinolone acetonide in orabase 0.1% compared to that in patients receiving *Centella asiatica* in orabase or placebo. Pain was significantly relieved after treatment in all study groups. No statistically significant differences in the pain scores were found within the three study groups at the end of treatment. In conclusion, the efficacy of *Centella asiatica* in orabase was less than that of triamcinolone acetonide in orabase 0.1% in the treatment of oral lichen planus and oral lichenoid lesions.

REFERENCES

1. Eisen D. The clinical features, malignant potential, and systemic associations of oral lichen planus: A study of 723 patients. J Am Acad Dermatol 2002; 46: 207-14.
2. Setterfield JF, Black MM, Challacombe SJ. The management of oral lichen planus. Clin Exp Dermatol 2000; 25: 176-182.
3. Lynch MA, Brightman VJ, Greenberg MS, editors. Burket's oral medicine: Diagnosis and treatment. 9th ed. Philadelphia: J.B. Lippincott; 1994.
4. Sugerman PB, Savage NW. Oral lichen planus: Causes, diagnosis and management. Aus Dent J 2002; 47(4): 290-297.
5. Castellanos JL. Gingival disorders of immune system. Medicina Oral 2002; 7: 271-83.
6. Thornhill MH. Immune mechanisms in oral lichen planus. Acta Odontol Scand 2001; 59: 174-7.
7. Dorrego MV, Correnti M, Delgado R, Tapia FJ. Oral lichen planus: immunohistology of mucosal lesions. J Oral Pathol Med 2002; 31: 410-4.
8. Porter SR, Kirby A, Olsen I, Barrett W. Immunologic aspects of dermal and oral lichen planus. A review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997; 83: 358-66.
9. Stoopler ET, Sollecito TP, DeRossi SS. Desquamative gingivitis: Early presenting symptom of mucocutaneous disease. Quintessence Int 2003; 34(8): 582-6.
10. Keratsaidis A, Schreurs O, Helgeland K, Axell T, Schenck K. Erythematous and reticular forms of oral lichen planus and oral lichenoid reactions differ in pathological features related to disease activity. J Oral Pathol Med 2003; 32: 275-81.
11. Wong L, Freeman S. Oral lichenoid lesions (OLL) and mercury in amalgam fillings. Contact Dermatitis 2003; 48: 74-9.

12. Carrozzo M, Gandolfo S. Review: The management of oral lichen planus. Oral Diseases 1999; 5: 196-205.
13. Sugerman PB, Savage NW, Zhou X, Walsh LJ, Bigby M. Oral lichen planus. Clin Dermatol 2000; 18: 533-9.
14. Brinkhaus B, Lindner M, Schuppan D, Hahn EG. Review Article. Chemical, pharmacological and clinical profile of the East Asian medical plant *Centella asiatica*. Phytomedicine 2000; 7(5): 427-48.
15. Edwards PC, Kelsch R. Oral lichen planus: Clinical presentation and management. J Can Dent Assoc 2002; 68(8): 494-9.
16. Mollaoglu N. Oral lichen planus: a review. Brit J Oral Maxillofacial Surg 2000; 38: 370-7.
17. Scully C, El-Kom M. Lichen planus: review and update on pathogenesis. J Oral Pathol 1985; 14: 431-58.
18. Jungell P. Oral lichen planus. A Review. Int J Oral Maxillofacial Surg 1991;20: 129-135.
19. Wood NK, Goaz PW. Differential diagnosis of oral lesions. 5th ed. St Louis: Mosby; 1997.
20. Epstein JB, Wan LS, Gorsky M, Zhang L. Oral lichen planus: Progress in understanding its malignant potential and the implications for clinical management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003; 96: 32-7.
21. Scully C, Beyli M, Ferreiro M, Ficarra G, Gill Y, Griffiths M *et al*. Update on oral lichen planus: Etiopathogenesis and management. Crit Rev Oral Biol Med 1998; 9(1): 86-122.
22. Rodriguez-Nunez I, Blanco-Carrion A, Garcia AG, Ray JG. Peripheral T-cell subsets in patients with reticular and atrophic-erosive oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001; 91: 180-8.
23. Sugerman PB, Savage NW, Walsh LJ, Zhao ZZ, Zhou XJ, Khan A, et al. The pathogenesis of oral lichen planus. Crit Rev Oral Biol Med 2002; 13(4): 350-65.
24. Krutchkoff DJ, Eisenberg E. Lichenoid dysplasia: A distinct histopathologic entity. Oral Surg Oral Med Oral Pathol 1985; 30: 308-15.

25. Van der Meij EH, van der Waal I. Lack of clinicopathologic correlation in the diagnosis of oral lichen planus based on the presently available diagnostic criteria and suggestions for modifications. J Oral Pathol Med 2003; 32: 507-12.

26. Rinaggio J, Neiders ME, Aguirre A, Kumar V. Using immunofluorescence in the diagnosis of chronic ulcerative lesions of the oral mucosa. Compendium 1999; 20(10): 943-60.

27. Silverman S. Oral lichen planus: A potentially premalignant lesion. J Oral Maxillofac Surg 2000; 58: 1286-8.

28. McCartan BE, McCreary CE. Guest editorial. What is the rationale for treating oral lichen planus?. Oral Dis 1999; 5: 181-2.

29. Buajeeb W, Pobrurksa C, Kraivaphan P. Efficacy of fluocinolone acetonide gel in the treatment of oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000; 89: 42-5.

30. Thongprasom K. Management of lichen planus [Online]. Faculty of Dentistry, Chulalongkorn University. Available from: http://www.odgt.net/ [Accessed 2005 Jan 10].

31. Scully C, El-Kabir M. *Candida* and oral candodosis: A review. Crit Rev Oral Biol Med 1994; 5(2): 125-57.

32. Ellepola ANB, Samaranayake LP. Oral candidal infections and antimycotics. Crit Rev Oral Biol Med 2000; 11(2): 172-98.

33. McIntyre GT. Oral candidosis. Dent Update 2001; 28: 132-9.

34. Gandolfo S, Richiardi L, Carrozzo M, Broccoletti R, Carbone M, Pagano M, et al. Risk of oral squamous cell carcinoma in 402 patients with oral lichen planus: a follow-up in an Italian population. Oral Oncol 2004; 40: 77-83.

35. Rodstrom P-O, Jontell M, Mattsson U, Holmberg E. Cancer and oral lichen planus in a Swedish population. Oral Oncol 2004; 40: 131-8.

36. Barnard NA, Scully C, Eveson JW, Cunningham S, Porter SR. Oral cancer development in patients with oral lichen planus. J Oral Pathol Med 1993; 22: 421-4.

37. Larsson A, Warfvinge G. Malignant transformation of oral lichen planus. Oral Oncol 2003; 39: 630-1.

38. Silverman S, Gorsky M, Lozada-Nur F, Giannotti K. A prospective study of findings and management in 214 patients with oral lichen planus. Oral Surg Oral Med Oral Pathol 1991; 72: 665-70.

39. Voute ABE, de Jong WFB, Schulten EAJ, Snow GB, van der Waal I. Possible premalignant character of oral lichen planus. J Oral Pathol Med 1992; 21: 326-9.

40. Silverman S, Bahl S. Oral lichen planus update: Clinical characteristics, treatment responses, and malignant transformation. Am J Dent 1997; 10: 259-63.

41. Mignogna MD, Muzio LL, Russo LL, Fedele S, Ruoppo E, Bucci E. Clinical guidelines in early detection of oral squamous cell carcinoma arising in oral lichen planus: a 5-year experience. Oral Oncol 2001; 37: 262-7.

42. Eisenberg E. Oral lichen planus: A benign lesion. J Oral Maxillofac Surg 2000; 58: 1278-85.

43. Holmstrup P, Thorn JJ, Rindum J, Pindborg JJ. Malignant development of lichen planus-affected oral mucosa. J Oral Pathol 1988; 17: 219-25.

44. Axell T, Pindborg JJ, Smith CJ, van der Waal I and an International Collaborative Group on Oral White Lesions. Oral White lesions with special reference to precancerous and tobacco-related lesions: conclusions of an international symposium held in Uppsala, Sweden, May 18-21 1994. J Oral Pathol Med 1996; 25: 49-54.

45. Van der Meij E, Schepman K-P, van der Waal I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: A prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003; 96: 164-71.

46. McCreary CE, McCartan BE. Clinical management of oral lichen planus. Brit J Oral Maxillofac Surg 1999; 37: 338-43.

47. Adcock IM. Corticosteroids: limitations and future prospects for treatment of severe inflammatory disease. Drug Discovery Today: Therapeutic Strategies 2004; 1(3): 321-8.

48. Seymour RA, Meechan JG, Yates MS. Pharmacology and dental therapeutics. 3th ed. Oxford: W.B. Saunders; 1999.

49. Huber MA. Oral lichen planus. Quintessence Int 2004; 35: 731-52.

50. Lozada-Nur F, Huang MZ. Open preliminary clinical trial of clobetasol proprionate ointment in adhesive paste for treatment of chronic oral vesiculoerosive diseases. Oral Surg Oral Med Oral Pathol 1991; 71: 283-7.

51. Rodstrom P-O, Hakeberg M, Jontell M, Nordin P. Erosive oral lichen planus treated with clobetasol proprionate and triamcinolone acetonide in orabase: a double-blind clinical trial. J Dermatol Treat 1994; 5: 7-10.

52. Carbone M, Conrotto D, Carrozzo M, Broccletti 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 fluocinolone. Oral diseases 1999; 5:44-9.

53. Carbone M, Goss E, Carrozzo M, Castellano S, Conrotto D, Broccoletti R, Gandolfo S. Systemic and topical corticosteroid treatment of oral lichen planus: a comparative study with long-term follow-up. J Oral Pathol Med 2003; 32: 323-9.

54. Thongprasom K, Luangjaemekorn 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.

55. Buajeeb W, Kraivaphan P, Pobrurksa C. Efficacy of topical retinoic acid compared with topical fluocinolone acetonide in the treatment of oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997; 83: 21-5.

56. Voute ABE, Schulten EAJM, Langendijk PNJ, Kostense PJ, van der Waal I. Fluocinonide in an adhesive base for treatment of oral lichen planus. Oral Surg Oral Med Oral Pathol 1993; 75: 181-5.

57. Hegarty AM, Hodgson TA, Porter SR. Fluticasone proprionate spray and betamethasone sodium phosphate mouthrinse: A randomized crossover study for the treatment of symptomatic oral lichen planus. J Am Acad Dermatol 2002; 47: 271-9.

58. Tyldesley WS, Harding SM. Betamethasone valerate aerosol in the treatment of oral lichen planus. Brit J Dermatol 1977; 96: 659-62.

59. Holbrook WP, Kristmundsdottir T, Loftsson T. Aqueous hydrocortisone mouthwash solution: clinical evaluation. Acta Odontol Scand 1998; 56: 157-60.
60. Zegarelli DJ. Multimodality steroid therapy of erosive and ulcerative oral lichen planus. J Oral Med 1983; 38(3): 127-30.
61. Drug facts and comparisons, 1999 edition. Missouri: J.B. Lippincott; 1999.
62. Anderson PO, Knoben JE, Troutman WG. Handbook of clinical drug data. International edition. 10th edition. New York: McGrawhill; 2002.
63. Lozada F. Prednisolone and azathioprine in the treatment of patients with vesiculoerosive oral diseases. Oral Surg 1985; 52(3): 257-60.
64. Sloberg K, Hersle K, Mobacken H, Thilander H. Topical tretinoin therapy and oral lichen planus. Arch Dermatol 1979; 115: 716-8.
65. Giustina TA, Stewart JCB, Ellis CN, Regezi JA, Annesley T, Woo TY, Voorhees JJ. Topical application of isotretinoin gel improves oral lichen planus. Arch Dermatol 1986; 122: 534-6.
66. Hersle K, Mobacken H, Sloberg K, Thilander H. Severe oral lichen planus: treatment with an aromatic retinoid (etretinate). Brit J Dermatol 1982; 106: 77-80.
67. Gorsky M, Raviv M. Efficacy of etretinate (Tigason) in symptomatic oral lichen planus. Oral Surg Oral Med Oral Pathol 1992; 73: 52-5.
68. Camisa C, Allen CM. Treatment of oral erosive lichen planus with systemic isotretinoin. Oral Surg Oral Med Oral Pathol 1986; 62: 393-6.
69. Bollag W, Ott F. Treatment of lichen planus with temarotene. The Lancet 1989; 21: 974.
70. Laurberg G, Geiger J-M, Hjorth N, Holm P, Hou-Jensen K, Jacobsen KU, et al. J Am Acad Dermatol 1991; 24: 434-7.
71. Ott F, Bollag W, Geiger J-M. Efficacy of oral low-dose tretinoin (all-*trans*-retinoic acid) in lichen planus. Dermatology 1996; 192: 334-6.
72. 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.

73. Frances C, Boisnic S, Etienne S, Szpirglas H. Effect of the local application of cyclosporine A on chronic erosive lichen planus of the oral cavity. Dermatologica 1988; 177:194-5.

74. 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.

75. Femiano F, Gombos F, Scully C. Clinical trial. Oral erosive/ulcerative lichen planus: preliminary findings in an open trial of sulodexide compared with cyclosporine (ciclosporin) therapy. Int J Dermatol 2003; 42: 308-11.

76. Lener EV, Brieva J, Schachter M, West LE, Wes DP. Successful treatment of erosive lichen planus with topical tacrolimus. Arch Dermatol 2001; 167: 419-22.

77. Morrison L, Kratochvil FJ, Gorman A. An open trial of topical tacrolimus for erosive oral lichen planus. J Am Acad Dermatol 2002; 47: 617-20.

78. Rozycki TW, Rogers RS, Pittelkow MR, McEvoy MT, el-Azhary RA, Bruce AJ, et al. Topical tacrolimus in the treatment of symptomatic oral lichen planus: A series of 13 patients. J Am Acad Dermatol 2002; 46: 27-34.

79. Lear JT, English JS. Erosive and generalized lichen planus responsive to azathioprine. Clin Exp Dermatol 1996; 21: 56-7.

80. Ho VC, Gupta AK, Ellis CN, Nickoloff BJ, Voorhees JJ. Treatment of severe lichen planus with cyclosporine. J Am Acad Dermatol 1990; 22: 64-8.

81. Walchner M. Topical tetracycline treatment of erosive oral lichen planus. Arch Dermatol 1999; 135: 92-3.

82. Ronbeck BA, Lind PO, Thrane PS. Desquamative gingivitis: Preliminary observations with tetracycline treatment. Oral Surg Oral Med Oral Pathol 1990; 69: 694-7.

83. Bagan JV, Silvestre FJ, Mestre S, Gisbert C, Bermejo A, Agramunt J. Oral Surg Oral Med Oral Pathol 1985; 60: 608-10.

84. Matthews RW, Scully C. Griseofulvin in the treatment of oral lichen planus: adverse drug reactions, but little beneficial effect. Ann Dent 1992; 1: 10-11.

85. Falk DK, Latour DL, King LE. Dapsone in the treatment of erosive lichen planus. Am Acad Dermatol 1985; 12: 567-70.

86. Beck H, Brandrup F. treatment of erosive lichen planus with dapsone. Acta Derm Venereol (Stockh) 1986; 66: 366-7.
87. Matthews RW, Pinkney RCN, Scully C. The management of intransigent desquamative gingivitis with dapsone. Ann Dent 1989; 48: 41-3.
88. Eisen D. Hydroxychloroquine sulfate (Plaquenil) improves oral lichen planus: A open trial. J Am Acad Dermatol 1993; 28: 609-12.
89. Hildebrand A, Kolde G, Luger TA, Schwarz T. Successful treatment of generalized lichen planus with recombinant interferon alfa-2b. Am Acad Dermatol 1995; 33: 880-3.
90. Lundstrom IMC, Anneroth GB, Holmberg K. *Candida* in patients with oral lichen planus. Int J Oral Surg 1984; 13: 226-238.
91. Lu S-Y, Chen W-J, Eng H-L. Dramatic response to levamisole and low-dose prednisolone in 23 patients with oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995; 80: 705-9.
92. Bogaert H, Sanchez E. Lichen planus: treatment of thirty cases with systemic and topical phenytoin. Int J Dermatol 1990; 29: 157-8.
93. Dereure O, Basset-Seguin N, Guilhou J-J. Erosive lichen planus: dramatic response to thalidomide. Arch Dermatol 1996; 132: 1392-3.
94. Grunwald MH, Amichai B. Dapsone-the treatment of infectious and inflammatory diseases in dermatology. Int J Antimicrobial agents 1996; 7: 187-92.
95. Popovsky JL, Camisa C. New and emerging therapies for diseases of the oral cavity. Dermatol Clin 2000; 18(1): 113-25.
96. Lundquist G, Foesgren H, Gajecki M, Emtestam L. Photochemotherapy of oral lichen planus. A controlled study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995; 79: 554-8.
97. Vedtofte P, Holmstrup P, Pindborg JJ. Surgical treatment of premalignant lesions of the oral mucosa. Int J Oral Surg 1987; 16: 656-64.
98. Loitz GA, Patrick J. Erosive lichen planus of the tongue treated by cryosurgery. J Oral Maxillofac Surg 1986; 44: 580-2.

99. Hodak E, Yosipovitch G, David M, Ingber A, Chorev L, Lider O, et al. Low-dose low-molecular-weight heparin (enoxaparin) is beneficial in lichen planus: a preliminary report. J Am Acad Dermatol 1998; 38: 564-8.

100. Rice PJ, Hamburger J. Oral lichenoid drug eruptions: their recognition and management. Dent Update 2002; 29: 442-7.

101. McCartan BE, McCreary CE. Oral lichenoid drug eruptions. Oral diseases 1997; 3: 58-63.

102. Raghu AR, Nirmala R, Sreekumaran N. Direct immunofluorescence in oral lichen planus and oral lichenoid reactions. Quintessence Int 2002; 33: 234-9.

103. Thornhill MH, Pemberton MN, Simmons RK, Theaker ED. Amalgam-contact hypersentivity lesions and oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003; 95: 291-9.

104. Ido T, Kumakiri M, Kiyohara T, Sawai T, Hasegawa Y. Oral lichen planus due to zinc in dental restorations. Contact Dermatitis 2002; 47: 51.

105. Pemberton MN, Sloan P, Thakker NS. Oral lichenoid lesions after hepatitis B vaccination. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000; 89: 717-9.

106. Dunsche A, Kastel I, Terheyden H, Springer ING, Christophers E, Brasch J. Oral lichenoid reactions associated with amalgam: improvement after amalgam removal. Brit J Dermatol 2003; 148: 70-6.

107. Vogel HG, De Souza N, D' Sa A. Effects of terpenoids isolated from *Centella asiatica* on granuloma tissue. Acta Therapeutica 1990; 16: 285-98.

108. Dabral PK, Sharma RK. Evaluation of the rule of Rumalaya and Geriforte in chronic arthritis – A preliminary study. Probe 1983; 22(2): 120-7.

109. Shukla A, Rasik AM, Jain GK, Shankar R, Kulshrestha DK, Dhawan BN. *In vitro* and *in vivo* wound healing activity of asiaticoside isolated from *Centella asiatica*. J Ethnopharm 1999; 65: 1-11.

110. Marquart FX, Bellon G, Gilery P, Randoux A, Brieu MA, Borel JP. Stimulation of collagen synthesis in fibroblast culture by an extract of Centella asiatica: specific effect on the free prolone pool. Biochimica et Bilphysica Acta 1989; 22(3): 55-7.

111. Coldren CD, Hashim P, Ali JM, Oh S-K, Sinskey AJ, Rha C. Gene expression changes in the human fibroblast induced by *Centella asiatica* triterpenoids. Planta Med 2003; 69: 725-32.

112. Ravokatra A, Loiseau A, ratismamanga-Urverg S, Nigeon-Dureuil M, Ratsimamanga AR. Action de I'asiaticoside triterpene pentacyclique retire de I'hydrocotyle madagascariensis sur les ulcers douodenaux cres par la mercaptoethylamine chez le rat wistar male. C R Acad Sc Paris 1974; 278: 2317-21.

113. Sakina MR, Dandiya PC. A psycho-neuropharmacological profile of *Centella asiatica* extract. Fitoterapia 1990; 61: 291-6.

114. Diwan PV, Karwande L, Singh AK. Anti-anxiety profile of Manduk Parni (*Centella asiatica*) in animals. Fitoterapia 1991; 3: 253-7.

115. Labadie RP, Nat JM, Kroes BH, Kosasi S, Berg AJ, Hart LA, et al. An ethnopharmacognostic approach to the search for immunomodulators of plant origin, Plant Med 1989; 55: 339-48.

116. Dhar ML, Dhar MM, Dhawan BN, Mehrotra BN, Ray C. Screening of Indian Plants for biological activity. Indian J Exp Bio 1968; 6: 232-44.

117. Arpaia MR, Ferrone R, Amitrano M, Nappo C, Leonardo G, del Guercio R. Effects of *Centella asiatica* extract on mucopolysaccharide metabolism in subjects with varicose veins. Int J Clin Pharm Res 1990; 4: 229-33.

118. Addy M, Embery G, Edgar WM, Orcsardson R. Tooth wear and sensitivity. 1st ed. London: Martin and Dunitz; 2002.

APPENDIX

Patient number	Previous treatments		Candidal culture	
	No	Yes	Negative	Positive
1		✓	✓	
2	✓		✓	
3	✓		✓	
4	✓		✓	
5		✓	✓	
6	✓			✓
7		✓	✓	
8		✓	✓	
9		✓	✓	
10		✓	✓	
11	✓		✓	
12	✓			✓
13	✓		✓	
14	✓			✓

Appendix A. Previous treatments and candidal culture at the beginning in patients receiving triamcinolone acetonide in orabase 0.1%

Patient number	Previous treatments		Candidal culture	
	No	Yes	Negative	Positive
1	✓			✓
2		✓	✓	
3		✓	✓	
4		✓	✓	
5		✓	✓	
6		✓	✓	
7		✓	✓	
8	✓		✓	
9	✓		✓	
10		✓	✓	
11		✓	✓	
12	✓			✓
13	✓			✓
14	✓		✓	

Appendix B. Previous treatments and candidal culture at the beginning in patients receiving *Centella asiatica* in orabase

Patient number	Previous treatments		Candidal culture	
	No	Yes	Negative	Positive
1		✓	✓	
2		✓	✓	
3	✓			✓
4		✓	✓	
5		✓	✓	
6	✓			✓
7		✓	✓	
8	✓		✓	
9	✓			✓
10		✓		✓
11	✓		✓	
12	✓		✓	
13	✓			✓
14	✓		✓	

Appendix C. Previous treatments and candidal culture at the beginning in patients receiving placebo

Patient number	Sex	Age (Years)	Diagnosis	Location	Duration (Months)
1	F	52	OLP	B	132
2	M	70	OLL	B	24
3	M	44	OLP	B,G	2
4	F	36	OLP	G	12
5	F	54	OLP	B,G	12
6	F	66	OLP	G,M	7
7	F	37	OLP	G	12
8	F	51	OLP	G	24
9	F	43	OLP	G	12
10	F	71	OLP	B,G	unknown
11	F	42	OLP	B,T	6
12	F	58	OLP	B,M	36
13	F	46	OLP	B,G,M	1
14	F	56	OLL	B	1

F: Female; M: Male; OLP: Oral lichen planus; OLL: Oral lichenoid lesions
B: Buccal mucosa; G: Gingiva; T: Tongue; M: Mucobuccal fold

Appendix D. Clinical data of patients receiving triamcinolone acetonide in orabase 0.1%

Patient number	Sex	Age (Years)	Diagnosis	Location	Duration (Months)
1	M	71	OLP	B,M	4
2	F	36	OLP	G	24
3	F	66	OLP	G,M	7
4	F	37	OLP	B,G	12
5	F	54	OLP	B,G	12
6	F	60	OLP	B,G,M	6
7	M	70	OLL	B,G,M	24
8	F	62	OLP	G,M	5
9	F	56	OLP	G	12
10	F	71	OLP	B,G	unknown
11	F	52	OLP	B	132
12	M	18	OLP	G,M	unknown
13	F	52	OLP	B	36
14	F	61	OLL	B	2

F: Female; M: Male; OLP: Oral lichen planus; OLL: Oral lichenoid lesions
B: Buccal mucosa; G: Gingiva; T: Tongue; M: Mucobuccal fold

Appendix E. Clinical data of patients receiving *Centella asiatica* in orabase

Patient number	Sex	Age (Years)	Diagnosis	Location	Duration (months)
1	F	78	OLL	B,T	3
2	F	32	OLL	B,M	60
3	F	44	OLP	G,M	6
4	F	71	OLP	B,G	unknown
5	F	52	OLP	B	132
6	F	56	OLP	G	12
7	M	71	OLP	B,M	4
8	F	42	OLP	G,M	3
9	F	55	OLP	B,G,M	6
10	F	54	OLP	B,G,M	12
11	F	42	OLP	B,T	3
12	F	43	OLP	B,M	5
13	F	58	OLP	B,M	36
14	F	46	OLP	B,G,M	1

F: Female; M: Male; OLP: Oral lichen planus; OLL: Oral lichenoid lesions
B: Buccal mucosa; G: Gingiva; T: Tongue; M: Mucobuccal fold

Appendix F. Clinical data of patients receiving placebo

Patient number	Pain scores Time		
	Beginning	Second week	Fourth week
1	0.4	0.1	0
2	4.7	4.2	3.2
3	6.3	3.9	1.9
4	6.7	3.5	2.5
5	3.4	0.4	0.2
6	2.5	1.7	1.1
7	1.7	0.2	0.2
8	2.4	1.2	0.1
9	6.8	6.8	5.9
10	2.8	1.9	0.7
11	6.6	4.5	1.2
12	6.1	4.8	3.1
13	5	3.9	1.8
14	3.7	1.3	0.5

Appendix G. Pain scores of patients receiving triamcinolone acetonide in orabase 0.1%

Patient number	Pain scores Time		
	Beginning	Second week	Fourth week
1	4.7	4.3	4.7
2	5.1	3.1	3.5
3	0.1	0	0
4	5.3	5.3	5.3
5	1.9	1	0.3
6	8.5	6.5	4.9
7	7.5	5.7	3.9
8	3.8	3.8	2.3
9	0.7	0.7	0.4
10	2.1	3.5	1.3
11	2	1.6	0.3
12	5.6	4.2	3.3
13	4.4	4	2.9
14	1.6	1.1	0.6

Appendix H. Pain scores of patients receiving *Centella asiatica* in orabase

Patient number	Pain scores Time		
	Beginning	Second week	Fourth week
1	8.1	5.2	1.6
2	5.8	5.4	2.9
3	6.7	5.6	5.6
4	2.5	1	0.5
5	0.1	0.3	0.6
6	1.2	0.4	0.1
7	4.2	2.1	0.4
8	3.8	3.6	3.4
9	2.6	2.6	2.6
10	3.4	2.4	1.6
11	8.4	6.6	3.6
12	1.4	1.4	1.4
13	3.9	2.5	2.3
14	3.8	1.9	1

Appendix I. Pain scores of patients receiving placebo

BIOGRAPHY

NAME	Miss Kattalee Kittiprasan
DATE OF BIRTH	2 October 1976
PLACE OF BIRTH	Songkla, Thailand
INSTITUTIONS ATTENDED	Mahidol University, 2000: Bachelor of Doctor of Dental Surgery Mahidol University, 2005: Master of Science (Oral medicine)
POSITION & OFFICE	Sawangdandin Hospital, Sakonakorn, Thailand. Position: Dentist
HOME ADDRESS	40/22 Soi Ladprao 23, Chatuchak, Bangkok, Thailand. Tel. (66) 0-2511-2378