
Current controversies in oral lichen planus: Report of an international consensus meeting. Part 2. Clinical management and malignant transformation

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Despite recent advances in understanding the immunopathogenesis of oral lichen planus (LP), the initial triggers of lesion formation and the essential pathogenic pathways are unknown. It is therefore not surprising that the clinical management of oral LP poses considerable difficulties to the dermatologist and the oral physician. A consensus meeting was held in France in March 2003 to discuss the most controversial aspects of oral LP. Part 1 of the meeting report focused on (1) the relationship between oral LP and viral infection, with special emphasis on hepatitis C virus (HCV), and (2) oral LP pathogenesis, in particular the immune mechanisms resulting in lymphocyte infiltration and keratinocyte apoptosis. Part 2 focuses on patient management and therapeutic approaches and includes discussion on malignant transformation of oral LP. (**Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100:164-78**)

Oral lichen planus (LP) is a chronic inflammatory oral mucosal disease of unknown cause. The clinical management of oral LP poses considerable difficulties to the dermatologist and the oral physician.¹

The authors met in France between March 9 and 15, 2003, to produce a consensus document based on the most recent literature published in peer-reviewed international journals. Some aspects of LP to be discussed

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were previously decided by the panel and assigned to each participant according to her/his field of expertise. During the meeting a report was presented by the author and discussed by the panel.

Selected articles published after March 2003 were included by the authors in the reference list.

The aspects of oral LP discussed and presented in the current 2-part review include viral infection and immunopathogenesis (Part 1)² and clinical management and malignant potential (Part 2).

THE MANAGEMENT OF ORAL LICHEN PLANUS

Although oral LP is often asymptomatic, the atrophic-erosive form can cause symptoms ranging from burning sensation to severe pain, interfering with speaking, eating, and swallowing.³⁻⁵ Patients with symptomatic oral LP often require therapy and should be treated if symptoms are significant.⁶

As oral LP is a chronic disease, the patient's medical history, psychological state, and treatment compliance, as well as possible drug interaction, must be considered when evaluating the cost effectiveness of any treatment modalities.⁷ When oral lichenoid lesions are suspected to be related to the use of a given drug,⁸ the medication should be discontinued whenever possible.

Plaque and calculus deposits are associated with a significantly higher incidence of erythematous and erosive gingival oral LP lesions,⁹ whereas good oral hygiene is essential and can enhance healing.^{10,11} Mechanical trauma of dental procedures, friction from sharp cusps, rough dental restorations, and poorly fitting

dental prostheses can be exacerbating factors of symptomatic oral LP and should receive attention. Furthermore, dental amalgam restorations can cause oral lichenoid lesions which may improve following replacement of amalgam with other restorative materials.¹²⁻¹⁶ Although it has been suggested that lesions in close anatomic contact with amalgam fillings in patients with positive patch tests to mercury compound should be replaced, resolution of the lichenoid area cannot be assured¹⁷ and even composite resin restorations can occasionally induce lichenoid lesions.¹⁸ Moreover, metal-ceramic crowns do not seem to facilitate the healing of the lesions to the same extent as the gold crowns,¹⁴ although some reports have highlighted many allergic reaction to gold salts, too.¹⁹⁻²²

The psychological profile of the oral LP patient should also be taken into account. Studies have reported higher levels of anxiety, greater depression, and increased psychic disorders in oral LP compared with a control group,²³ and stress is one of the most frequent causes of acute exacerbations in oral LP patients.^{4,24}

Various treatment regimens (Table I) have been designed to improve management of symptomatic oral LP, but a permanent cure is not yet possible.^{7,25} Several treatments lack adequate controlled studies. Few randomized controlled trials have been carried out, usually involving small numbers of patients and reporting for the most part favorable responses to the studied treatment, suggesting publication bias.^{26,27} Because of the great heterogeneity of the published reports, many data cannot be directly compared and meta-analysis is problematic.²⁷ Curiously, several suggested treatment modalities are also suspected to induce lichenoid lesions. Treatment approaches to oral lichen planus are suggested in Fig 1.

Corticosteroids

Systemic corticosteroids. Systemic corticosteroids are probably the most effective treatment for patients with diffuse erosive oral LP or multisite disease, but the literature on their use is limited to nonrandomized clinical trial. Both methyl prednisolone²⁸ and prednisone²⁹ have been employed for recalcitrant severe erosive oral LP. Systemic prednisone can be used to control the ulcers and erythema in oral LP but it is not better than treatment with topical triamcinolone acetonide alone.³⁰ Interestingly, topical corticosteroids have been found to be equally or more effective than systemic corticosteroids or the combination of the two.^{31,32} Systemic corticosteroids may be indicated in patients whose condition is unresponsive to topical steroids or in patients with mucocutaneous disease and in high doses (1.5-2 mg/kg/daily), but adverse effects are possible even with short courses.^{6,32}

Table I. Empirical treatments for oral lichen planus (modified from Carrozzo and Gandolfo³)

<i>Corticosteroids</i>	
<i>Topical</i>	
	Betamethasone phosphate
	Betamethasone valerate*
	Clobetasol propionate*
	Fluocinolone acetonide
	Fluocinonide*
	Fluticasone propionate
	Hydrocortisone hemisuccinate
	Triamcinolone acetonide
<i>Systemic</i>	
	Prednisone
	Methylprednisolone
<i>Retinoids</i>	
<i>Topical</i>	
	Fenretinide
	Isotretinoin*
	Tazarotene*
	Tretinoin*
<i>Systemic</i>	
	Acitretin**
	Etretinate
	Isotretinoin
	Temarotene
	Tretinoin
<i>Immunosuppressive agents</i>	
	Azathioprine
	Cyclosporin*
<i>Others</i>	
	Amphotericin A
	Basiliximab
	Diethylthiocarbamate
	Dapsone
	Doxycycline
	Enoxaparin
	Glycyrrhizin***
	Griseofulvin [#]
	Hydroxychloroquine sulphate [#]
	Interferon [#]
	Levamisole [#]
	Magnetism
	Mesalazine [#]
	Phenytoin [#]
	Photopheresis
	Psychotherapy [#]
	PUVA ^{#§}
	Reflexotherapy
	Surgery [#]
	Tacrolimus
	Thalidomide***

*Placebo-controlled studies confirm their efficacy in oral lichen planus.

**A placebo-controlled study of 65 patients with LP, some of whom had mucous membrane involvement, has been carried out. However, the authors did not specify clearly neither the percentage of the study population with oral involvement nor the response criteria for oral cavity lesions.¹⁰⁹

***In a study, glycyrrhizin therapy was compared with patients only having dental cleaning.

[#]Treatment modalities suspected to induce lichenoid lesions.

[§]A controlled study with split-mouth design has been carried out.¹²⁹

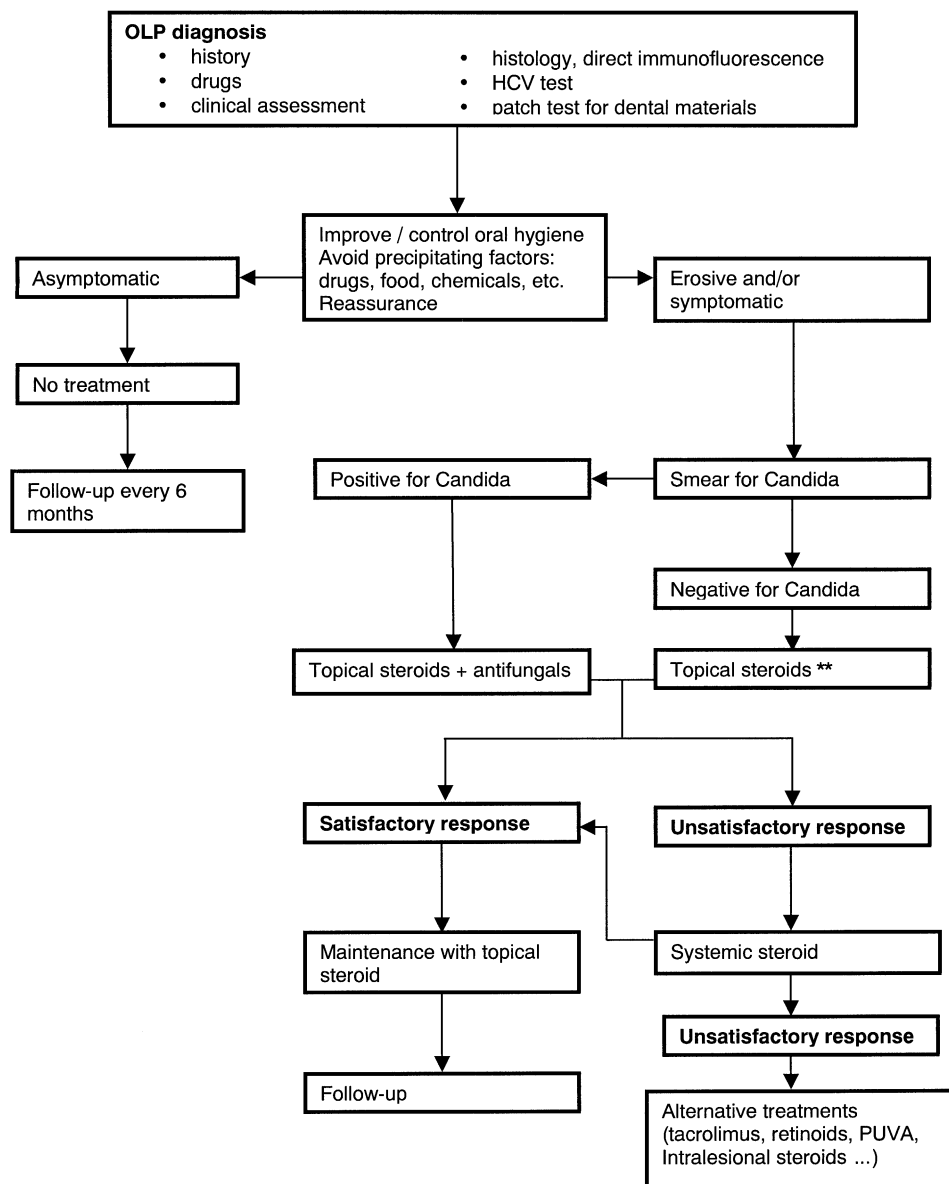


Fig 1. Clinical management of oral lichen planus.

*Topical corticosteroids (Table II).*³³⁻⁴⁴ Topical corticosteroids are widely used in the treatment of oral LP to reduce pain and inflammation. Triamcinolone acetonide is commonly used either in orabase or lozenge.^{41,45} An oral suspension of triamcinolone has also been used with beneficial effect.³⁰ Hydrocortisone hemisuccinate in aqueous solution seems of little benefit in treating oral LP,⁴⁴ whereas betamethasone valerate pellets³³ or aerosol³⁴ showed some effectiveness. High-potency steroid mouthwashes such as disodium betamethasone phosphate or clobetasol propionate, can be used in widespread oral LP but these may cause a significant systemic absorption leading to a pitui-

tary-adrenal axis suppression.⁴⁰ Recently, fluticasone propionate spray has been used effectively in the short-term management of symptomatic oral LP, but 10% of the patients did not tolerate such treatment for more than 3 weeks.³⁵ Topical corticosteroids in adhesive paste, such as betamethasone valerate, clobetasol, fluocinolone acetonide, fluocinonide, and triamcinolone acetonide have been widely used.^{36,38,41-43} The more potent fluorinated steroids can be very effective and include fluocinonide 0.05%,^{31,42} and fluocinolone acetonide 0.1%.⁴¹ Fluocinonide 0.05% and fluocinolone acetonide 0.1% have been found to be effective in the treatment of severe oral LP that has failed to respond to

Table II. Reports of trials of topical corticosteroids in the management of oral LP (modified from Carrozzo and Gandolfo 1999³)

Drug	Class/potency of drug*	Reference	Patients (n)	Results (%)			Duration (weeks)	Study type
				CR	PR	NR		
Betamethasone valerate	5	Cawson 1968 ³³	30	43	23	34	2-48	Open
Betamethasone sodium phosphate**	7	Tyldesley 1977 ³⁴	11	64	9	27	8	Placebo-controlled
		Hegarty et al 2002 ³⁵	44	—	73	27	6	Comparative
Clobetasol propionate	1	Lozada-Nur et al 1991 ³⁶	9	56	22	22	2	Open
		Sardella et al 1998 ^{37***}	14	57	22.5	22.5	4	Comparative
		Carbone et al 1999 ³⁸	20	75	25	—	24	Placebo-controlled, Comparative
		LoMuzio et al 2001 ³⁹	24	100	—	—	2	Comparative
Fluocinolone acetonide	4	Gonzalez-Moles et al 2002 ⁴⁰	30	93	—	7	48	Open
		Thongprasom et al 1992 ⁴¹	19	68	unknown	unknown	4	Comparative
Fluocinonide	3	Lozada and Silverman 1980 ⁴²	56	52	48	—	2	Placebo-controlled
		Voute et al 1993 ⁴³	20	20	60	20	9	Placebo-controlled
		Carbone et al 1999 ³⁸	20	25	65	10	24	Placebo-controlled, Comparative
Fluticasone propionate	3 [#]	Hegarty et al 2002 ³⁵	44	—	80	20	6	Comparative
Hydrocortisone hemisuccinate	7	Holbrook et al 1998 ⁴⁴	54	48	37	15	2-4	Open
Triamcinolone acetonide	4	Thongprasom et al 1992 ⁴¹	19	42	unknown	unknown	4	Comparative

CR, complete response; PR, partial response; NR, no response.

*Class 1 is the most potent; class 7 is the least potent.²²²

**Betamethasone sodium phosphate has a potency comparable to dexamethasone sodium phosphate.

***Sardella et al used clobetasol in ointment alone; all the other studies on clobetasol, excepting Gonzales-Moles et al, used clobesol in various adhesive media.

[#]According to the Italian Pharmacopeia (PFN 2003),²²³ fluticasone propionate 0.05% ointment or cream has a potency comparable to fluocinonide, but in the study of Hegarty et al (2002)³⁵ it has been administered as spray.

other medications.^{41,43} Fluocinolone acetonide 0.1% in orabase has been shown to be more effective than a similar triamcinolone acetonide 0.1% preparation⁴¹ with no serious side effects. Moreover, the effectiveness of various forms of topical fluocinolone acetonide applications in patients with oral LP in a 2-year treatment resulted in complete remission of 77.3%, 21.4%, and 17.0% of patients in the fluocinolone acetonide in orabase (FAO), fluocinolone acetonide in solution (FAS), and FAS/FAO groups, respectively.⁴⁶ This drug can also be effectively used in the management of lichenoid lesion flare in patients with systemic diseases such as hypertension, heart disease, or diabetes mellitus with no serious side effects.

Clobetasol propionate in aqueous solution, ointment, or orabase has also been shown to be effective in oral LP.^{37-40,47} Clobetasol can be more effective than fluocinonide in improving lesions,⁴⁷ and the long-term use of clobetasol (6 months) may help to control the disease, offering substantial disease-free periods in 65% of the patients after 6 months of follow-up.³⁸

Although there are some reports of systemic absorption and adrenal suppression from super-potent topical steroids in the treatment of chronic skin disorders,⁴⁸⁻⁵⁰ adrenal suppression has not been found in long-term oral application of topical corticosteroids such as

fluocinonide 0.05%, fluocinolone acetonide 0.1%, and clobetasol 0.05%.^{38,41,47,51} Acute pseudomembranous candidiasis is the only common side effect from topical corticosteroid therapy.^{41,43,47} This can be prevented with antifungal (miconazole gel) alone or with chlorhexidine mouthwashes.³⁸

Intralesional corticosteroids. Intralesional injections of hydrocortisone,⁵² dexamethasone,⁵³ triamcinolone acetonide,⁵⁴⁻⁵⁶ and methylprednisolone⁵⁷ have been used in the treatment of oral LP. However, the injections can be painful, are not invariably effective, and have a localized effect such as mucosal atrophy.¹

In summary, systemic corticosteroids should be reserved for acute exacerbations or multiple or widespread lesions. Topical treatments can be used with systemic corticosteroids to reduce the systemic side effects or can be used alone.

Antifungals

Candida albicans is present in about 37% of oral LP lesions.^{58,59} Symptoms of oral LP may be exacerbated by candidal overgrowth or infection, while antifungal treatment of erosive lesions with *Candida* can change the lesions to the reticular form.^{5,60} Theoretically the use of antifungal treatment in some cases of oral LP could reduce the potential of *Candida albicans* to

produce carcinogenic N-nitrosobenzylmethylamine.⁶¹ The antifungal griseofulvin has been used⁶²⁻⁶⁵ but others have reported no improvement during treatment of oral LP with griseofulvin and, on the contrary, the condition became more severe in some patients.⁶⁶⁻⁶⁸

Clinical improvement with relief of symptoms has been reported following use of amphotericin B,⁶⁹ nystatin, and azole antifungals.^{5,30,70} Miconazole gel is found to be effective in the treatment of candidiasis eruptions during topical steroid therapy in every case of oral LP⁴¹ and is useful as an adjunctive therapy with topical steroids.³⁸

Cyclosporin (Table III)⁷¹⁻⁸⁹

Cyclosporin is a polypeptide that inhibits the transcription of several cytokine genes, thereby suppressing T-cell cytokine production. It may be beneficial in the treatment of oral LP.^{71,72,76} Some studies have suggested that cyclosporin is effective applied either topically^{71,80,88} or in the form of mouthrinse,^{73-75,83,86,87} but others have reported little benefit^{79,82,85} or no significant improvement.^{77,78,81,84,89}

In oral LP patients, systemic absorption is probably low and most studies did not detect cyclosporin in peripheral blood. Although many studies have claimed the effectiveness of cyclosporin, the disadvantages of this medication are bad taste, transient burning sensation on initial application, and high cost.^{74,75,82,88} Comparative study of cyclosporin and triamcinolone acetonide in orabase in the treatment of oral LP has not found any significant difference of remission rates,⁹⁰ and another recent comparative study found that clobetasol in adhesive medium is more effective than cyclosporin in the same medium.⁹¹ Cyclosporin can be an alternative to conventional treatments for initial control of oral LP. However, it should not be considered as a first drug of choice because of the high cost of long-term treatment and the availability of effective alternatives. Severe side effects of systemic cyclosporin, such as hypertension and nephrotoxicity, preclude its use for oral LP.

Retinoids

Systemic and topical forms of retinoids have been used in the treatment of oral LP.⁹²⁻⁹⁷ Topical 0.1% vitamin A rapidly eliminated white lesions of oral LP but all cases relapsed 2-5 weeks after discontinuation of treatment.⁹⁸ Isotretinoin gel 0.1% and tretinoin ointment can produce significant improvement in patients with oral LP. Only transient burning sensations or irritation on initial application have been reported.^{99,100} Moreover, following treatment with topical tretinoin, histologic examination demonstrated that keratinization may decrease significantly or even

disappear.¹⁰¹ Topical fenretinide, has proved to be beneficial in the treatment of oral LP with minimal side effects¹⁰² but is not readily available. However, a 0.05% retinoic acid gel was less effective than fluocinolone acetonide 0.1% in orabase.¹⁰³ Systemic etretinate has been used successfully for the treatment of severe oral LP.^{94,104} In erosive oral LP, etretinate (25-75 mg daily for 8 weeks) produced only slight improvement with frequent and severe side effects.¹⁰⁵ When etretinate provided effective treatment for severe oral LP, relapses were commonly seen following discontinuation of therapy.^{94,106} Common side effects of etretinate include cheilitis, generalized pruritus, hair loss, dryness of mucous membranes, paronychia,^{94,105,107} and increased serum transaminase levels.⁹⁵

Systemic isotretinoin has been used successfully in severe erosive oral LP refractory to conventional therapies¹⁰⁸ but relapses occurred within 2 months after the drug was stopped.⁹⁶ In a double-blind placebo-controlled study, acitretin was more effective than placebo.¹⁰⁹ Tazarotene is a retinoid analogue with few adverse effects and has been shown to be effective.¹¹⁰ An oral low dose of tretinoin (all-*trans*-retinoic acid) has been used in recalcitrant oral LP with complete and partial remissions and without marked side effects.¹¹¹

Very recently, a new topical retinoid, tazarotene, has been used for the treatment of oral LP and demonstrated to be helpful in hyperkeratotic oral LP in a small randomized placebo-controlled study.¹¹²

Because of possible side-effects of systemic retinoids and low remission rates, the primary use of retinoids is dissuaded.¹¹³ Both systemic and topical retinoids should be used as adjuvant therapy only.¹¹⁴

Tacrolimus

Tacrolimus is a potent immunosuppressive agent, inhibiting T-cell activation at 10-100 times lower concentration than cyclosporin.¹¹⁵ Notably, topical tacrolimus seems to penetrate skin better than topical cyclosporin. This drug used topically can control symptoms and significantly improve refractory erosive oral LP.^{116,117} Local irritation is the most common adverse effect.¹¹⁸ Tacrolimus ointment 0.1% is well tolerated and appeared to be effective in erosive oral LP that did not respond to topical steroids.¹¹⁹ Although topical tacrolimus is effective and well tolerated, some oral LP patients have noted flare-ups soon after stopping the treatment.¹²⁰ Recently, the treatment of chronic erosive oral LP with low concentrations of tacrolimus has been found to yield a rapid and important palliative effect,¹²¹ but all patients relapsed after 12-month follow-up in this study.

Table III. Reported trials of topical cyclosporin in the management of oral lichen planus (modified from Carrozzo and Gandolfo, 1999³)

Author	Patients (n)	Formulation	Daily dose (mg)	Duration of treatment	Results	Side effects
Frances et al 1988 ⁷¹	4	Topical	25	4	CR/PR	No
Balato et al 1989 ⁷²	7	Mouthrinse	50-100	8	CR/PR	Unknown
Eisen and Ellis 1990 ⁷⁵	16	Mouthrinse	1500	8	CR/PR	Transient burning sensation
Eisen et al 1990 ⁷⁴	6	Mouthrinse	1500	8	CR	Transient burning sensation
Eisen et al 1990 ⁷³	6	Mouthrinse	500	8	CR	No
Ho et al 1990 ⁷⁶	4	Mouthrinse	600	8-12	CR	Unknown
Veller and Catalano 1991 ⁷⁷	2	Topical	100	12	NR	Unknown
Ho and Conklin 1991 ⁷⁸	4	Mouthrinse	600	8-12	NR	Unknown
Levell et al 1991 ⁷⁹	7	Mouthrinse	1500	4	NR	Unknown
Gombos et al 1992 ⁸⁰	6	Topical	48	8	CR(?) / PR(?)	Unknown
Itin et al 1992 ⁸¹	7	Topical	126	8	NR/PR	Unknown
Porter et al 1993 ⁸²	6	Mouthrinse	1500	8-10	PR	Transient burning sensation, deposits between teeth
Pacor et al 1994 ⁸³	14	Mouthrinse	500	12	CR	No
Voute et al 1994 ⁸⁴	9	Topical	unknown	3	NR	No
Becherel et al 1995 ⁸⁵	8	Topical	50	12	NR/CR	No
Harpenau et al 1995 ⁸⁶	15	Mouthrinse	500	4	CR	No
Lopez-Lopez and Rosello-Llabres 1995 ⁸⁷	?	Mouthrinse	250	8	CR?	Unknown
Epstein and Truelove 1996 ⁸⁸	14	Topical	unknown	4	PR/NR	Transient burning sensation
Jungell and Malmstrom 1996 ⁸⁹	7	Mouthrinse	450	4	NR/PR	Unknown

CR, complete response; PR, partial response; NR, no response.

Ultraviolet irradiation

Photochemotherapy with 8-methoxypsoralen and long-wave ultraviolet light (PUVA) has been used successfully in the treatment of skin lesions and cutaneous LP.^{122,123} It was first used in the treatment of recalcitrant oral LP.¹²⁴ Eighty-seven percent of patients treated with ultraviolet-A, without a systemic or topical photosensitizer, improved significantly.¹²⁵ Some studies have indicated that PUVA therapy might also have therapeutic effects.¹²⁶ To avoid PUVA side effects, photosensitization with topical 0.01% trioxsalen can be used for the treatment.¹²⁷ Although oral mucosa seems more resistant than skin to phototoxic damage,¹²⁸ PUVA with 8-methoxypsoralen has many side effects such as nausea, dizziness, eye symptoms, paraesthesia, and headache.¹²⁹ Photochemotherapy may be useful for severe forms of erosive oral LP that do not respond to conventional treatment.¹³⁰ Moreover, one matter of concern is that PUVA therapy has been shown to have oncogenic potential.¹³¹ Further study of PUVA therapy for oral LP is needed.

Miscellaneous treatments

Antibiotics. Tyldesley successfully treated severe and painful erosive oral LP with 2% aureomycin mouthwash.⁵⁵ Tetracycline (doxycycline) was also found to be useful in the treatment of gingival lesions in some reports,^{132,133} but it has shown little benefit in others. However, antibiotics are not recommended at the moment for routine treatment oral LP.

Antimalarials. Hydroxychloroquine sulfate showed some clinical efficacy in 9 out of 10 oral LP patients.¹³⁴ An excellent response to 3 months treatment with chloroquine phosphate was also reported in patients with lower lip lichen planus.¹³⁵ However, antimalarial agents have been also implicated as a cause of oral lichenoid reactions.¹³⁶

Azathioprine. The efficacy of azathioprine in the treatment of erosive and generalized oral LP has been reported.^{137,138} Dermatologists commonly use this drug for the treatment of severe recalcitrant diseases in the oral cavity.¹³⁹ Azathioprine has potent immunosuppressive effects, including bone marrow suppression, and

long-term use may increase the risk of internal malignancy.¹⁴⁰ However, the results are no better than systemic steroids alone or systemic steroids in conjunction with topical steroids.³¹

Dapsone. Dapsone has been used in the treatment of erosive oral LP with some benefit.^{141,142} It should be considered in resistant cases, particularly when severe erosive lesions are present.¹⁴³ Significant adverse effects such as haemolysis and headache have been reported.¹⁴⁴ Generally, the use of dapsone in the treatment oral LP is precluded.

Glycyrrhizin. The successful treatment of oral LP patients with chronic hepatitis C infection by glycyrrhizin was reported.¹⁴⁵ Glycyrrhizin given intravenously in oral LP patients with HCV infection was clinically effective.¹⁴⁶ Because this drug has known hepatoprotective effects, its utility in oral LP patients requires further investigation.

Interferon. Two small noncontrolled studies have suggested that a topically applied gel preparation containing human fibroblast interferon (HuIFN-beta) and interferon-alpha (IFN-alpha) cream may improve erosive oral LP.¹⁴⁷ A further study of HuIFN-beta reported high therapeutic effectiveness in treating oral LP.¹⁴⁸ Interestingly, development and exacerbation of oral LP during and after IFN-alpha therapy for HCV infection have been reported¹⁴⁹⁻¹⁵² although systemic IFN-alpha (3-10 million UI thrice weekly) was successfully used to treat oral LP in patients with and without HCV infection.¹⁵³⁻¹⁵⁵

Levamisole. Levamisole has been used as an immunomodulator in oral LP.¹⁵⁶ The combination of levamisole and Chinese medicinal herbs can achieve complete remission more than either therapy given alone.¹⁵⁷ Combined therapy with a low dose of systemic steroid may also be helpful in the control of severe erosive oral LP.²⁵ However, levamisole may occasionally itself induce lichenoid lesions.¹⁵⁸

Mesalazine. Mesalazine (5-aminosalicylic acid) is a relatively new drug widely used in the treatment of inflammatory bowel diseases. When topical mesalazine was compared with clobetasol propionate for the treatment of symptomatic oral LP, it was as effective as the topical steroid.³⁷ Interestingly, mesalazine is able to induce formation of lichenoid lesions.¹⁵⁹

Phenytoin. There has been only 1 report of phenytoin therapy in oral LP. Two out of 4 oral LP cases had complete healing with this drug.¹⁶⁰ No further study has confirmed the efficacy of phenytoin or its side effects, although phenytoin may also induce lichenoid lesions.¹⁶¹

Reflexotherapy. There has been 1 report of reflexotherapy in the treatment of oral LP.¹⁶²

Surgery. Surgical excision has been recommended for isolated plaques or nonhealing erosions because it provides excellent tissue specimens for histopathologic confirmation of diagnosis and may cure localized disease. Surgical excision^{163,164} as well as cryosurgery¹⁶⁵ has been used. Cryosurgery has been used successfully in cases of erosive oral LP resistant to most treatment modalities.¹⁶⁶ CO₂ laser has been used in the treatment of multicentric lesions or in difficult areas of oral LP.¹⁶⁷⁻¹⁷⁰ Although resolution of oral LP lesions following cryosurgery has been reported in a few instances without complications except for recurrences,¹⁷¹ lesions may develop in the healing wounds and recur in scars, producing even more symptoms. Free soft-tissue grafts have also been used for localized areas of erosive oral LP,¹⁷² and the symptomatic oral LP completely disappeared following treatment with a free gingival graft after 3.5 years follow-up.¹⁷³

ORAL LICHEN PLANUS AND CANCER

Since the first report in 1910 of a gingival cancer diagnosed in a patient with oral LP, a large number of similar cases have been published. They include single case reports, as well as case series and large follow-up studies. Most of these cases have been analysed by 2 independent groups of researchers adopting the same criteria^{174,175} (Table IV). Subsequently, a number of cases have been accepted as sufficiently documented to be indicated as real cases of malignant transformation in oral LP.

Malignant potential of oral lichen planus

According to the current definition, precancerous lesion is "a morphologically altered tissue in which cancer is more likely to occur than in apparently normal counterpart."¹⁷⁶ Thus the best way to establish the putative premalignant nature of oral LP would be a prospective follow-up study of a group of affected patients and a group of unaffected individuals including smokers and nonsmokers. Unfortunately such a study is not available. In fact, because of the low incidence of oral cancer in the general population and in oral LP patients, a properly designed study of that kind would require a very large number of participants (a few thousand at least) and a long follow-up (not less than 5 years).

Therefore, the best evidence currently available on the potentially malignant nature of oral LP is from follow-up studies and retrospective incidence studies^{4,6,177-194} (Table V).

The frequency of oral cancer among oral LP patients reported in 3 of the 4 retrospective studies available from 1985 to the present was $\leq 1.5\%$, with the follow-up from 4.5 to 7.5 years. The retrospective studies are

quite heterogeneous and differ in source of data (clinical records and data base of histological reports), inclusion criteria, length of follow-up, design, and geographical origin. However the results of these studies move in a relatively narrow range (0%-5.3%) and do not contrast with those from prospective studies (Table V).

In support of the malignant potential of oral LP, a large retrospective study of 2,071 patients affected by cutaneous LP, of unknown oral status, showed a high incidence of oral cancer (including lip cancer), with a relative risk of 5.9% (95% confidence interval 2.5-11.4).¹⁹⁵ Another study that must be mentioned is a case-control study from China based on the characteristics of 404 pairs that found a strong association between oral cancer and oral LP, which was found in 41/404 cancers and 2/404 controls.¹⁹⁶

On the basis of these data, the transformation rate of oral LP appears to be around 1% over 5 years. Such an incidence is much higher than any figure reported in medical literature for the oral cancer incidence in the general population (www.dep.iarc.fr) and strongly supports the malignant potential of oral LP. This same conclusion was reached from an analysis of the available literature by an evidence-based approach.¹⁹⁷ However, it was noted that this figure (1% in 5 years) is not compatible with the epidemiology of oral LP and oral cancer. In fact, an oral LP prevalence of 1% and a transformation rate of 0.2% per year would mean that nearly every oral cancer should develop from oral LP lesions,¹⁷⁵ an hypothesis that was confuted by some studies where very few cases of oral cancers with simultaneous presence of oral LP were found.^{182,182,184,184,196}

As mentioned previously, articles published in 1978 and 1999^{174,175} reviewed all the papers reporting cases of cancer in patients affected by oral LP, rejecting 93 and 66% of them respectively. For this analysis the authors adopted strict criteria based on diagnosis, history, follow-up, and tobacco exposure. Although this can be considered an excellent initiative to encourage a better reporting of such cases, some of the criteria may not be adequate. Many cases were rejected because of lack of histologic pictures, often due to publishing requirements, or because the reviewers did not agree with the authors on the histologic diagnosis, implying that an assessment of few microphotographs (often in black and white) can be more accurate than the examination of a pathologic slide at the microscope. Another criteria used to exclude many cases, in particular in the 1978 paper, was the concurrence of oral LP and tobacco use, because exposure to such a well known risk factor was considered enough to allocate to smoking the only causative role for cancer. It is possible that some of the cases described can be linked mainly to tobacco use but

Table IV. Krutchkoff's criteria for the assessment of scientific literature on oral lichen planus: malignant transformation¹⁷⁵

A. Original diagnosis

Clinical diagnosis must have been properly verified, with histopathologic evidence demonstrating at least the last 2 of these 4 features.

1. Hyperkeratosis or parakeratosis
2. Saw-toothed rete pegs
3. Superficial infiltrate of lymphocytes
4. Basal cell liquefaction

B. History and follow-up

1. Clinical and historical features of alleged transformation must have been adequately described (information such as age, gender, precise location, and clinical description of lesion are necessary).
2. Reported transformation should have had proper follow-up (minimum of 2 years), with all changes in clinical features properly recorded.

C. Tobacco exposure

Tobacco habits should have been properly documented to help distinguish between true malignant transformations and convectional carcinomas occurring in the mouths of patients who happen to have lichen planus.

to rule out a putative risk factor on the basis of a presence of another appears inappropriate—risk factors are not etiologic agents and such an approach would not allow the identification of new risk factors.

Lichen planus and lichenoid dysplasia

Following the 1978 review of the published cases of malignant transformation of oral LP, which rejected the vast majority of cases, it was suggested that the high incidence of oral cancer in patients with a diagnosis of oral LP was due to a condition with distinctive histopathologic characteristics, termed lichenoid dysplasia (LD). The assumption for such a proposal was that any departure from normal epithelial maturation and growth altogether excludes a diagnosis of oral LP,¹⁹⁸ although consensus on such criteria has never been reached, and some authors consider dysplasia a very common feature of oral LP.¹⁹⁹ In addition it must be pointed out that inflammation itself, the basic pathologic feature of oral LP, can elicit histologic features similar to dysplasia, making a distinction between oral LP and LD even more difficult.

The entity LD might correspond to 2 groups of conditions: those with clinical features similar to oral LP but dysplasia at the histological level; and those with lichenoid microscopic features (band-like lymphocytic infiltration in particular) and clinical features which do not resemble classic oral LP (unilateral distribution, absence of reticular lesions). The former could represent an early phase in the malignant transformation of oral LP, while the latter could represent various clinical

Table V. Studies of oral LP malignant transformation from 1985 to present

	Oral LP cases	Malignant transformations	Mean follow-up (range)	Data source
<i>Prospective studies</i>				
Silverman et al 1985 ¹⁷⁷	570	7 (1.2%)	5.6 yrs	
Murti et al 1986 ¹⁷⁸	702	3 (0.4%)	5.1 yrs	
Holmstrup et al 1988 ¹⁷⁹	611	9 (1.5%)	7.5 yrs (1-26)	
Salem 1989 ¹⁸⁰	64	4 (6.25%)	3.2 yrs	
van der Meij et al 2003 ⁸¹⁸¹	173	3 (1.7%) [‡]	2.6 yrs (0.5-6)	
<i>Retrospective studies</i>				
Voute et al 1992 ¹⁸²	113	3 (2.6%)	7.8 yrs (0.5-21)	clinical records
Barnard et al 1993 ¹⁸³	241	8 (3.3%)	unclear	clinical records
Brown et al 1993 ¹⁸⁴	193	0	8 yrs (2-9)	clinical records
Gorsky et al 1996 ¹⁸⁵	157	2 (1.3%)	>4 yrs	clinical records
Vescovi and Gennari 1996 ¹⁸⁶	71	3 (4.2%)	5 yrs	clinical records
Silverman and Bahl 1997 ¹⁸⁷	95	3 (3.2%)	6.1 yrs (1-20)	clinical records
LoMuzio et al 1998 ¹⁸⁸	263	14 (5.3%)	5.7 yrs (2-10)	clinical records
Rajenthiran et al 1999 ¹⁸⁹	832	4 (0.5%)	>1.5 yrs	clinical records
Chainani-Wu et al 2001 ⁶	229	4 (1.7%)	unclear	clinical records
Cowan et al 2001 ¹⁹⁰	383	0	Na	histologic data base
Eisen 2002 ⁴	723	6 (0.8%)	4.5 yrs (0.5-8)	clinical records
Rode and Kogoj-Rode 2002 ¹⁹¹	55	0	unclear [#]	clinical records
Yaacob et al 2002 ¹⁹²	19	1*	3.6 yrs (1-6)	clinical records
Gandolfo 2et al 004 ¹⁹³	402	9 (2.2%)	4.9 yrs	clinical records
Rodstrom et al 2004 ¹⁹⁴	1028	5 (0.5%)**	6.8 yrs	clinical records

*Lichenoid reaction.

**Higher than expected incidence (difference statistically different).

‡All from the oral lichenoid lesion group.

§62 patients with oral lichen planus and 111 with oral lichenoid lesions.

#Up to 25 years.

conditions that may have lichenoid histopathology including lichenoid reactions, lupus erythematosus, leukoplakia, erythroleukoplakia, and proliferative verrucous leukoplakia (PVL). PVL, particularly in the early stages, can have features, both clinical and histologic, that can be confused with oral LP, frequently shows dysplastic changes, and is characterized by a high malignant transformation rate.

Extraoral lichen planus and cancer

Although less reported than oral counterparts, cases of squamous cell carcinoma arising from skin or nonoral mucosal surfaces affected by LP have been described. Nearly all sites can be involved, including skin,^{195,200} anal mucosa,²⁰¹ vulvar mucosa,^{202,203} and penis.²⁰⁴ However, a Swedish retrospective study¹⁹⁵ did not find a significant risk of squamous cell carcinoma of the skin in patients with cutaneous LP (relative risk 1.2; 95% confidence interval 0.4-2.5).

Lichenoid lesions and cancer

The most interesting data on lichenoid lesions and malignancies are those from patients who underwent allogeneic bone marrow transplantation and developed oral graft versus host disease (GVHD). Oral GVHD is clinically and histologically indistinguishable from oral LP. Case reports²⁰⁵⁻²⁰⁸ and large studies²⁰⁹⁻²¹¹ describe numerous episodes of oral cancers (mainly squamous

cell carcinoma) in patients with oral GVHD. A large study that investigated the incidence of solid tumors in 20,000 bone marrow transplantation patients found that oral cancer had the highest risk among cancers, being 11.1 times more frequent than expected.²¹¹ Chronic GVHD was also a risk factor for the development of solid tumors in other similar studies.^{209,210} The significant risk factors for oral squamous cell carcinoma were chronic GVHD, limited-field irradiation and male sex. In 1 of these studies, head and neck cancer was the only solid cancer observed in a group of 78 patients undergoing bone marrow transplantation for Fanconi anemia. In this study, the frequency of such tumors was 167 times higher than expected.²¹⁰ Clearly, bone marrow transplantation patients have numerous risk factors for malignancies (primary immunodeficiencies, immunosuppressive treatments, viral infections, and maybe genetic predisposition to cancer) that do not allow a comparison with oral LP patients; however, the similarity of the oral conditions and the apparent common tendency to transform are worthy of careful consideration.

Other lichenoid lesions that can undergo malignant transformation include discoid lupus erythematosus, in particular of the lip,²¹²⁻²¹⁴ amalgam-associated lichenoid reactions,²¹⁵ and oral lichenoid lesions of unknown origin.²¹⁶

Interestingly, in the most recent prospective study on premalignant potential of oral LP¹⁸¹ all cases of malignant transformation involved lesions that the authors included in the group of oral lichenoid lesions because they did not fulfill both clinical and histologic criteria for oral LP.

Effects of treatment for oral LP on the incidence of oral cancer

Patients affected by oral LP are often subjected to medical treatment for long periods. The drugs of first choice are immunosuppressive agents. Drugs used in oral LP include corticosteroids used locally or systemically, cyclosporin, azathioprine, and retinoids. The possible effect of such treatments on malignant transformation of oral LP is not clear.

Immunosuppressive agents affect the severity and progression of oral LP, but theoretically they could also trigger malignant transformation. For example, cyclosporin can promote cancer progression, both by a direct cellular effect and by an effect on the host's immune cells.²¹⁷ Unfortunately only sparse data are available on long term effects of treatment for oral LP on its malignant potential. But in a recent study of oral LP patients treated mostly with topical and/or systemic steroids, therapeutic modalities did not affect the risk of malignant transformation.¹⁹³ Some data are also available from bone marrow transplantation patients. Azathioprine for the treatment of chronic GVHD was a significant risk factor for the development of solid tumors (17/18 of which were squamous cell carcinomas),²¹⁰ although this finding was not completely confirmed by others.^{209,211}

Identification of patients with oral lichen planus at risk of malignant transformation

In some studies reporting oral LP malignant transformation, it was suggested that particular clinical presentations of oral LP might have a higher malignant potential. In particular, erosive and plaque-like forms of oral LP have been considered most likely to transform to cancer, although evidence for such an hypothesis is lacking. Furthermore, the putative role in oral LP transformation of well known risk factors for oral cancer (tobacco and alcohol) has been properly evaluated in a single study, suggesting that alcohol and tobacco or their interaction cannot explain the excess risk for oral cancer found for oral LP.¹⁹³

The identification of high-risk lesions has been investigated extensively in other oral diseases, particularly leukoplakia. Two of the most promising investigative techniques, DNA content and loss of heterozygosity (LOH), have been tested in oral LP lesions. DNA content could predict malignant trans-

formation, even in nondysplastic lesions. Only 3 patients with oral LP were included in this study, but none had aneuploid lesions (the high-risk profile) nor underwent malignant transformation.²¹⁸ In 2 studies employing LOH, the authors compared the frequency of LOH of oral LP lesions with other malignant and potentially malignant lesions and dysplastic lichenoid lesions.^{219,220} The results showed that oral LP lesions do not demonstrate a high-risk LOH profile when compared with the other conditions. Unfortunately it is not known whether the oral LP lesions studied did or did not undergo malignant transformation.

Screening of oral lichen planus patients

Two recent papers investigated the potential benefits of screening oral LP patients for oral cancer. One concluded that there is not evidence to support a screening program purposely designed, although it could be useful to exploit "existing resources" such as routine dental visits.²²¹ The second study worked from the assumption that screening would identify all oral cancers in oral LP patients at stage I. The authors calculated the cost effectiveness of 2 different screening programs, one involving specialists and another based on intervention by general dentists. The study concluded that such intervention would cost \$1,265,229 and would save 23.68 lives (\$53,430 per life). It must be stressed that the calculation was based on an oral LP prevalence of 1% and an annual malignant transformation rate of 0.2%, figures that have been questioned by the same research group.¹⁷⁵

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