Immunopharmacology and Immunotoxicology

ISSN: 0892-3973 (Print) 1532-2513 (Online) Journal homepage: http://www.tandfonline.com/loi/iipi20

Oral lichen planus: update on etiopathogenesis, diagnosis and treatment

Vito Crincoli, Maria Beatrice Di Bisceglie, Michele Scivetti, Alberta Lucchese, Simona Tecco & Felice Festa

To cite this article: Vito Crincoli, Maria Beatrice Di Bisceglie, Michele Scivetti, Alberta Lucchese, Simona Tecco & Felice Festa (2011) Oral lichen planus: update on etiopathogenesis, diagnosis and treatment, Immunopharmacology and Immunotoxicology, 33:1, 11-20, DOI: 10.3109/08923973.2010.498014

To link to this article: http://dx.doi.org/10.3109/08923973.2010.498014

Published online: 06 Jul 2010.

Immunopharmacology and Immunotoxicology, 2011; 33(1): 11–20

informa healthcare

REVIEW ARTICLE

Oral lichen planus: update on etiopathogenesis, diagnosis and treatment

Vito Crincoli[1], Maria Beatrice Di Bisceglie[1], Michele Scivetti[1], Alberta Lucchese[1], Simona Tecco[2], and Felice Festa[2]

[1]*Department of Dentistry and Surgery, University of Bari, Bari, Italy, and* [2]*Department of Dentistry and Surgery, University of Chieti, Pescara. Italy*

Abstract

Lichen planus is an inflammatory mucocutaneous disorder. Skin, oral and genital mucosal surfaces, scalp, and nails can be affected. Its development is chronic, with a possible malignant degeneration. Spontaneous remission is rare. Although the etiology of oral lichen planus is still unclear, there is evidence that it is a complex immunologic disease mediated by cytotoxic cells directed against basilar keratinocytes and resulting in vacuolar degeneration and lysis of basal cells. In long-standing, atrophic and erosive forms, the treatment is usually aimed at relieving pain and may include immunosuppressive agents, especially corticosteroid, topical cyclosporin, or tacrolimus, topical and systemic retinoids. However, the use of these drugs may be accompanied by several side effects. For this reason clinicians, currently, have focused their attention to new biological agents which provide selective immunological results with less side effects than generic immunosupressants.

Keywords: *Lichen planus; therapy; biologics*

Introduction

Lichen planus (LP) is an inflammatory mucocutaneous disorder of established immune-mediate pathogenesis. It commonly affects the mucosa of the oral cavity, but other sites can be involved, namely the skin, scalp (resulting in alopecia), nails, glans penis, vulvar, vaginal, esophageal, and conjunctival mucosae.[1–3] The disease most often occurs in middle-aged patients with a prevalence ranging from 0.5 to 2%.[4,5] Females are usually affected (65% of all patients).[4] Its development is chronic, with a possible malignant degeneration.[2] Spontaneous remission is rare.

Clinically, oral lichen planus (OLP) lesions are frequently bilateral but not always symmetrical. Buccal mucosa, dorsum of tongue and gingiva are usually affected. Gingival clinical appearance has often been described as "desquamative gingivitis."[4] Six clinical variants have been described[6]: reticular, including white striations (Wickham's striae), papular, plaque-like, atrophic or erythematous and erosive, including ulcerations and bullae. These forms can often coexist in various combinations.

Reticular lesions are commonly asymptomatic and often discovered during routinary oral examination. They are characterized by keratotic striae (Wickham's striae) that determine the occurrence of network or loop-like lesions. These striae may be surrounded by erythematous borders. Buccal mucosa is the most affected site, usually bilaterally.[7] However, striae may be present on tongue (lateral border), gingiva and lips.

Papular lesions consist of small white papules (0.5–1.0 mm), often coexisting with other clinical variants.[8]

Plaque lesions have a similar appearance to leukoplakia, from which differ for multifocal distribution. Plaques may be slightly elevated or flat and smooth. Dorsum of tongue and buccal mucosa are the most affected sites. This form is more common among tobacco smokers.[9]

Address for Correspondence: Prof. Vito Crincoli, Dipartimento di Odontostomatologia e Chirurgia, Università degli Studi di Bari, Piazza G. Cesare 11, 70124 Bari, Italy. E-mail: v.crincoli@doc.uniba.it

(Received 09 March 2010; revised 26 April 2010; accepted 31 May 2010)

ISSN 0892-3973 print/ISSN 1532-2513 online © 2011 Informa Healthcare USA, Inc.
DOI: 10.3109/08923973.2010.498014 http://www.informahealthcare.com/ipi

Atrophic form is characterized by the presence of erythematous areas, often surrounded by white striae. It may be associated with erosive or reticular forms. It's usually localized on adherent gingiva. The patient may report burning sensation, disgeusia and pain which can interfere with eating, speech and swallowing.

In the erosive form the affected areas are ulcerated and combined with atrophic features. Ulcerations are covered by a fibrinous plaque or pseudomembrane with irregular borders, from which reticular or finely radiating keratotic striae may arise. The clinical appearance of lesions may change from week to week.

Differential diagnoses include several disorders such as oral lichenoid reactions (OLR). They may be considered as a disease by itself or an exacerbation of a pre-existing OLP.[10] Oral mucosa and skin may be affected. A variety of factors are known to be associated with OLR (Table 1). A recent international consensus proposed the classification of ORL into three main groups[11]: (1) oral lichenoid contact lesions (OLCL); (2) oral lichenoid drug reactions (OLDR); (3) oral lichenoid lesions of graft-versus-host disease (OLL-GVHD).

OLCL are the result of an allergic contact stomatitis (delayed immune-mediate hypersensitivity). Clinical features suggestive for OLCL include their proximity to dental restorations (most commonly amalgam).[7] Some studies have reported resolution of the lesions on cessation of exposure to the causative factors.[12]

In OLDR, oral and/or cutaneous lesions develop after taking certain medications such as oral hypoglycemic agents, angiotensin–converting enzyme inhibitors and non-steroidal anti-inflammatory agents.

Finally, OLL-GVHD is a clearly defined entity which arise in patients with acute or, more commonly, chronic GVHD.

Clinically, lichenoid lesions may show a wide range of features including asymptomatic white reticular striae and plaques or painful erythematous or ulcerated areas. They have a tendency to be unilateral.[13]

Other diseases, such as leukoplakia and lupus erythematous (LE) must be taken in account for differential diagnosis.

Etiology and pathogenesis

Although the etiology of OLP is still unclear, there is evidence that it is a complex immunologic disease mediated by cytotoxic cells directed against basilar keratinocytes (KCs) and resulting in vacuolar degeneration and lysis of basal cells.

The immunohistology of OLP resembles that described for delayed-type hypersensitivity reactions and chronic GVHD. Lesions are result of T-cell-mediated immune damage in which cytotoxic $CD8^+$ T cells induce the apoptosis of basal cells of epithelium, the target cells in OLP.[14]

The primary event in the pathogenesis of disease is the interaction between endogenous or exogenous agent (allergens, drugs, viruses) with KCs.

Local production of interferon-γ (IFN-γ) by $CD8^+$ lymphocytes upregulates major histocompatibility complex (MHC) class I and induces MHC class II expression by KCs. Altered KCs antigens are recognized by langerhans cells (LC) and presented to T-lymphocytes either locally or distally through their passage to lymphnodes.

Degranulation of mucosal mast cells (MCs) and macrophage activation releases tumor necrosis factor (TNF-α), which has an important function in mucocutaneous T-lymphocyte homing.

MCs degranulation may by provoked by drugs involved in lichenoid reaction, neuropeptides secreted from nerves affected by electrical potentials (galvanic effects), trauma, infection (herpes viruses), psychological stress.[14]

TNF-α promotes the induction of the following adhesion molecule expression by endothelial cells and KCs: endothelial leukocyte adhesion molecule-1, intercellular adhesion molecules (ICAM) and vascular-cell adhesion molecule-1. The induction of adhesion molecule expression determines the initiation of lymphocytic infiltration which characterizes OLP.

T-lymphocytes migrate from extravascular to epithelium where remain through adhesive interactions between lymphocyte function-associated antigen-1 (LFA-1) on T cells and ICAM-1 expressed on KCs and LC. Here, lymphocytes influence further development and extension of lesions through their products such

Table 1. Factors associated with lichenoid drug reactions (OLR).

Systemic drugs	Dental materials	Other factors
Antimalarials	Amalgam	Mechanical trauma of dental procedures
Non-steroidal-anti-inflammatory drugs	Resine	Heat and irritants from cigarettes
Angiotensin–converting enzyme inhibitors	Composite	Friction from sharp cusps
Diuretics	Metals	Rough dental restorations
B-blockers		Poorly fitting dental prosthesis
Oral hypoglycemic		
Gold salts		Lip chewing
Penicillamine		Stressss
Antiretrovirals		Genetics
		Liver disease/hepatitis C virus

as histamine releasing factor which promotes MCs degranulation and IFN-γ.

IFN-γ promotes: expression of ICAM-1 by endothelial cells, expression of ICAM-1 and MHC class II on keratynocytes, upregulation of MHC class II and CD4 antigen expression on intraepithelial LC.

So, modified keratynocyte surface antigens are the target for cytotoxic T-cells which trigger keratynocytes apoptosis. Besides, damaged keratynocytes release cytokines with stimulatory effects on LC differentiation and which may also serve as chemotactic and growth factors for T-lymphocytes.

To gain a better understanding of the genetic risk factors, many authors evaluated associations between several gene polymorphisms and OLP. Genetic TNF-α and IFN-γ polymorphisms have been demonstrated to contribute to OLP susceptibility and to influence the progression of the disease.[15]

Fujita et al.[16] suggest an association between OLP and carriers of the TNFR2 ± 587 gene polymorphism. Sequence-specific PCR assay showed a significantly higher frequency of T/T genotype within the first intron of IFN-γ gene promoter and of the A allele at the –308 TNF-α polymorphisms. These polymorphisms increase the production of the respective cytokine.[17]

The absence of interleukin-4 (IL-4), IL-10, and TGF-β secretion by OLP lesional T cells[18] suggests that this Th1 cytokine bias may be genetically induced and influence OLP development.[15]

In particular, the higher IFN-γ production could be considered an important risk factor for OLP lesions development. Besides, the cytokine polymorphisms seem to influence the clinical presentation of the pathology. Carrozzo et al.[15] in fact, demonstrated that the OLP patients with skin involvement showed the –308 TNF-α G/A genotype with higher rate (82%) compared with patients with exclusive oral lesions (30%). This finding suggests that the joint presence of cutaneous lesions could be related to the higher TNF-α production.

Possible etiologic factors, like hepatitis C virus infection (HCV) has been suggested.[19]

The pathogenetic link between LP and HCV is still unclear. However, molecular mimicry between the virus and host epitopes is doubtful as well as viral factors (genotype or viral load).[19]

HCV immunologic pressure rather than direct HCV infection of epithelial cells seem to be involved as suggested by the Th1 cytokine environment sustaining the oral lesions.[13]

Specifically, the association between HCV and this extrahepatic manifestation has been related to the HLA-DR6 allele. In particular, the presentation of HCV-peptides by HLA-Dr6 alleles to CD4 T-lymphocytes could be responsible for the oral mucosa damage.[20] Thus, also the geographic heterogeneity of this association should be explained by genetic differences among populations.

Systemic drugs, such as non-steroidal anti-inflammatory agents, penicillamine, β-blockers, hypoglycemic drugs, methyldopa, gold salts, allopurinol, chlorpropamide, antihypertensives, diuretics, ACE inhibitors, antiretroviral medications have been related to lichenoid reactions.[21,22] These drugs may precipitate a latent pathology or exacerbate a previous disorder rather than causing the disease.

Histopathology

Definitive diagnosis of OLP should be based on histological confirmation of a representative biopsy coupled with attention to the clinical appearance of the lesion. However, several studies undelined a lack of clinicopathologic correlation in the diagnostic assessment of OLP.[23] Thus, there are several oral lesions that resemble lichen planus or that even are indistinguishable from lichen planus clinically and histopathologically, but having a distinct etiology. Occasionally, it is difficult, if not impossible, to arrive at an accurate diagnosis. Because the presently available histopathological criteria of OLP are not truly reproducible, a final diagnosis of OLP can not be made on histopathological grounds alone.[24] Histological diagnostic criteria have been proposed by to identify OLP and biologically different conditions that exhibit lichenoid features (Table 2).[25] All lesions that resemble OLP but do not meet criteria mentioned in Table 2 are defined OLR.

Table 2. Oral lichen planus: histological criteria and exclusionary features.

Essential features
Signs of "liquefaction degeneration" in the basal cell layer
Presence of well-defined bandlike zone of cellular infiltration confined to the superficial part of the connective tissue, consisting mainly of T-lymphocytes
Normal epithelial maturation pattern (absence of epithelial dysplasia)
Other nonrequisite features
"Candle-dripping" or "saw-tooth"-like rete ridge conformation
Parakeratosis
Civatte bodies
Separation of epithelium from lamina propria due to basal cell destruction
Exclusionary features
Atypical cytomorphology
Nuclear enlargement or hyperchromasia
Prevalent dyskeratosis
Increased number of mitotic figures; aberrant mitosis
Blunt rete ridges
Disordered stratification
Heterogeneous lichenoid infiltrate (deep extension below superficial stroma or perivascular infiltration)

Direct immunofluorescence (DIF) studies may be helpful in disease differentiation for cases with no specific clinical or histologic characteristics, or with ambiguous features of other diseases, such as lupus erythematous (LE).[26]

The most common immunoreactant at the dermoepidermal junction (DEJ) is fibrin, which is the best indicator in the diagnosis of LP.[27] It may be present alone or combined with other immunoreactants such as C3, IgG, IgM, and IgA.[28]

Within the basal cell layer, degenerating basal KCs form colloid (civatte, hyaline, or cytoid) bodies that appear as homogenous eosinophilic globules. The ultrastructure of colloid bodies suggests that they are apoptotic KCs.

DIF pattern of cytoid bodies (CBs) in OLP shows a tendency to cluster in groups of 10 or more. This feature may be useful in distinguishing LP from LE, because, in the latter condition, Ig deposits exhibit a more linear arrangement.[29]

The combination of fibrin deposition at the DEJ and fluorescent CBs is more characteristic of LP than LE, even if identical deposits of Igs in CBs, C3, or linear fibrin at the DEJ may be found both in LE and LP.[30]

However, C3 deposition occurs more frequently in LE than in LP where anti-C3 may be seen in a faint, fine, granular, or discontinuous linear pattern and presence of IgM is more suggestive of LE than LP.[28]

Rhodus et al.[31] have proposed that future diagnostic tools for OLP lesions could include cytokine profiling of involved tissues. The authors detected the level of NF-κB dependent cytokines, TNF-α, IL-1-α, IL-6, and IL-8 in tissue transudates directly from lesions of OLP and showed that their concentration was significantly higher than in tissue transudates of controls. Furthermore all ratios of cytokines, TNF-α/IL-6, IL-1/IL-6, and IL-8/IL-6 in OLP patients were decreased significantly, compared with that of controls, probably because the increase of IL-6 was far more extent than TNF-α, IL-1-α, IL-8. Rhodus concluded suggesting the possibility that a Th2-dominated immune response does occur in a subgroup of OLP patients. Considering that modulation of Th1/Th2 imbalance is becoming a new therapeutic strategy of some autoimmune diseases, for example, IL-4 in psoriasis, anti-CD4 monoclonal antibody in experimental arthritis,it may be considered a useful assay to monitor disease activity and therapeutic efficacy in OLP lesions.

Malignant transformation

The possible malignant transformation of OLP is subject of controversial opinions in literature. Krutchkoff et al.[32] in 1978 reviewed 223 previous cases of OLP with cancerous progression and concluded that only 15 of them were sufficiently documented. Many reports, in fact, lacked historical data regarding prior carcinogen exposure (e.g. tobacco, arsenicals, irradiation, thorium) and microscopic confirmation of clinical diagnoses. Besides, in some cases carcinomas developed in areas anatomically remote from the OLP lesions. Apart these documentary shortcoming, Krutchoff et al. demonstrated that there were no malignant transformation in those cases in which exposure to carcinogens could be excluded and concluded that malignant change is triggered by external factor and is not the end point of a natural process. They stated that some of the reported OLP cases developing oral cancer were not OLP but rather dysplastic lesions with lichenoid features.

Also van der Meij et al.[33] supported the hypothesis that patients with OLL present an increased risk of oral cancer development compared with OLP subjects. They affirmed that risk factors are smoking and alcohol intake and presence of a combination of lesions, for example plaque-type forms mixed to atrophic ones, probably because these lesions may predispose the mucosa to damage from carcinogenic agents more than normal oral mucosa.

Gandolfo et al.[34] on the other hand, showed that patients with OLP had a significantly increased risk of oral squamous cell carcinoma. The tongue ("oral cancer-prone site") seems to be the main site of cancer occurrence,[35] followed by mid-line of the palate, gingiva and lips.[36] The risk of cancer evolution is higher in woman[34] than in man, between the sixth and seventh decades of life.[35] The median interval between OLP diagnosis and cancer diagnosis ranges from 20.8 months to 10.1 years, although the highest risk is between 3 and 6 years after OLP diagnosis. Some infections may be involved in malignant transformation such as Candida albicans infection. It has been suggested that strains of C. albicans are able to catalyze the formation of the carcinogen *N*-nitrosobenzylmethylamine. Also variations in diet, symptoms-induced,[34,37] and therapy-related immunosuppression[33] could promote malignant metamorphosis.

Clinically, carcinomas arising from OLP are mainly exophytic keratotic lesions,[38] even if sometimes they show endophytic growth pattern.[39] A feature of carcinomas that appear on OLP is their tendency to multiplicity. Mignogna et al.[40] found that 29% of patients with carcinoma on OLP presented two or three independent neoplastic lesions (19% with a second tumor, 10% with two metachronous tumors). Histopathologically, most lesions are well-differentiated squamous carcinoma.[41] About the prognosis of patients presenting neoplasia, Mignogna et al.[42] reported 100% 3-year and 97% 5-year survival.

They recommend[42] a strict follow-up with inspection of head and neck limphonodes every 2 months during 5–9 months after oral cancer diagnosis, when the risk of metastasis or second primary tumor is maximum.

van Der Meij et al.[43] recommend a careful biannual follow-up for early diagnosis of any neoplastic

transformation, even if there is no agreement about this frequency.

However, malignant evolution cannot be easily discovered in all patients and this reflects a rapid progression from intraepithelial neoplasia to invasive carcinoma. Furthermore, the screening for oral cancer in OLP patients has a significant impact on the final costs and effectiveness considering that a recall system of all patients with OLP requires economic resources and the malignant potential of OLP is most likely very low.[44]

Therapy

At the present, there is no specific cure for OLP. If lesions are symptomless. treatment is generally not required.[45] Patients are only advised to return regularly for review, or sooner if they get symptoms.

In long-standing, atrophic and erosive forms, the treatment is usually aimed at relieving pain and may include: good oral hygiene, careful inspection of dental restorations to minimize frictional contact, antibacterial mouthwash (e.g. chlorhexidine), antifungal agents (nystatin oral suspension, miconazole gel or amphotericin lozenges), topical, intralesional, and systemic administration of immunosuppressive agents, especially corticosteroids,[45,46] topical cyclosporin, or tacrolimus,[47,48] topical and systemic retinoids,[49] antimalarials,[50] azathioprine, photochemotherapy.[51]

Topical application of corticosteroids (triamcinolone, fluocinolone acetonide, β-methasone valerate, clobetasol propionate) can be helpful for initial treatment and also for maintenance therapy. They may be administered as ointments, pastes, lozenges, mouthwashes, or inhalers.[52,53]

Clobetasol propionate ointment, a steroid 1600 times more potent than fluocinolone, has proved to be effective.[54] Adhesive bases (occlusive dressings) may be employed to enhance the effectiveness of topical treatment and to provide a prolonged exposure time of the oral mucosa to the active drug. However it needs a careful follow-up for adrenal suppression risk and development of secondary candidiasis. For this reason, cortisol levels must be checked at 3 and 6 months after beginning of therapy and salivar cytological samples must be collected for culture.

Systemic steroids are requested for recalcitrant lesions with severe signs and symptoms.[55] Prednisolone is generally employed. In this case, short-term, high-dosage is the most effective form (30–60 mg daily for 2–3 weeks).[56] The most common side effects are represented by gastrointestinal upset, mood alteration, polyuria, insomnia, changes in blood pressure, and blood glucose.[56,57] Topical or systemic treatment with synthetic retinoids have been used in the management of OLP and appear to have some benefit, although less than with topical steroids.[58] They should be considered as second-line therapy with antikeratinizing and immunomodulating effects,[59] with transient improvements. Adverse reactions and flare ups are common upon withdrawal of treatment.[59]

Several studies have evaluated the efficacy of cyclosporine, considering that OLP is a T-cell-mediated pathology and this drug targets the helper T-cell. However, the benefits derived from use of cyclosporine A have been demonstrated only in some cases and are dose-related.[60–62]

Five milliliter Sandimmune peroral formulation (100 mg/mL) may be used as oral mouthwash, even if cyclosporine is characterized by high molecular mass that interferes with mucosa penetration. For this reason, the successful employment of this agent could be related to its systemic absorption. However, cyclosporine causes nephrotoxic effects, hypertension and neurologic dysfunction.[63]

Also mycophenolate mofetil (MMF) has been employed for treatment of OLP. It is a new immunosuppressive agent introduced for treatment of autoimmune-anti-inflammatory skin disorders and also for chronic GVHD in patients with bone marrow transplantation.[64–66] It specifically and reversibly inhibits the proliferation of activated T cells by interfering with de novo purine synthesis by inhibiting type II inosine monophosphate dehydrogenase, an enzyme expressed in both stimulated T- and B-lymphocytes. It is well absorbed orally but is rapidly conjugated to glucuronide and eliminated in the urine. Suspected side effects related to its use are represented by increased risk of infections and lymphoproliferative malignant neoplasms.

Although its potency is equal to that of azathioprine, MMF, at moderate dosage, appears to be more effective than azathioprine in treatment of cutaneous LP.[67] This is probably due to the fact that in addition to its cytostatic effect on lymphocytes, MMF has also anti-inflammatory properties exerted by inhibition of leukocyte recruitment and adhesion to endothelial cells. MMF has been used for treatment of severe, erosive-ulcerative oral and genital lichen planus recalcitrant to other systemic therapies.[68] It induced complete, long-lasting remissions without flare ups over a follow-up period of up to 4 years. However, the improvement of lesions was noticed only after 4–6 week of therapy and this is probably related to the mechanism of action of the drug. No short- or long-term side effects were documented, except minor gastrointestinal disturbances after commencement of therapy.

Lundqvist et al.[69] carried out an open trial with Methotrexate, which has an anti-inflammatory and immunomodulating activity, supplemented with steroid ointments for severe erosive lichen. Four patients were given methotrexate in a dosage of 10–15 mg/week for

about 17 months and they all improved their symptoms. The authors concluded that methotrexate was a well-tolerated and effective treatment for severe erosive lichen. However, the delay of benefits onset is of several weeks. For this reason, it is necessary to motivate the patients to continue treatment until full improvement of signs and simptoms is obtained.

Also Tacrolimus has been used for management of chronic erosive OLP (CEOLP).[70] It is a hydrophobic, polycyclic macrolide immunosuppressant employed for prevention of the rejection of organ transplants.[71,72] On a cellular level, the mechanism of action of tacrolimus is closely related to that of cyclosporin A, acting by inhibiting IL-2 production by T-lymphocytes.[63,73] However, it is a smaller molecule with a better penetration than cyclosporine A.[74] The carrier for tacrolimus may be represented by petrolatum ointment whose anti-inflammatory action has been evaluated in patients with atopic dermatitis[75] or white soft paraffin.[76]

The results of clinical trials confirm that statistically significant improvement in symptoms occurs within 1 week of commencement of therapy. However, a relapse of lesions is noticed after drug suspension. For this reason, a maintenance therapy to control the disease is generally recommend.[77,78] Animal studies and case reports in humans,[79] have reported that long-term therapy with tacrolimus may increase the risk to development of malignant tumors such as squamous cell carcinoma, cutaneous sarcoma, and malignant melanoma. This is probably due to an inhibition of immune competent cells which prevent the development of cancer. In particular has been noted that tacrolimus alters mitogen-activated protein kinase and p53 pathway.[80] The results is an activation of extracellular signal-regulated kinases in neuronal cells and inhibition of the induction of p53 after apoptotic stimuli. Also the ratio Bax/Bcl-2 appears to be altered subsequent to tacrolimus therapy.

In three randomized clinical trials[81–83] 1% pimecrolimus cream was tested for erosive OLP treatment. Its structure and action resemble tacrolimus. Like tacrolimus, pimecrolimus is a topical calcineurin inhibitor which acts inhibiting dephosphorylation of nuclear factor of activated T cell by calcineurin and thus, reducing T-cell cytokine production. However, unlike tacrolimus, it has a weaker immunosuppressing capacy. Pimecrolimus seems to be effective for oral erosive lichen planus management as demonstrated by a reduction of ulceration, erythema, and VAS scores. However, the presence of systemic levels of pimecrolimus after mucosal applications necessitates long-term follow-up because it seems that long-term application is required to maintain clinical improvement.

Recently, rapamycin has been employed for treatment of recalcitrant CEOLP.[84] This drug has both antitumor and immunosuppressive properties. Similarly to other immunosuppressive agents such as tacrolimus and cyclosporine, it passively diffuses across the cell membrane and then binds to a cytosolic receptor called FKBP-12, particular isoforms' FK 506 BP (binding protein) belonging to the family of immunofillins. Once bound to the cytoplasmic receptor FKBP-12, it interacts with the protein complex called "mammalian target of rapamycin (mTOR), blocking its functions and thus inhibiting the synthesis of IL-2 dependent cell progression from G1 to S phase of the cell cycle. The immunosuppressant activity of rapamycin is expressed at cellular level primarily through the inhibition of T- and B-lymphocytes activity. The drug inhibits, in a dose-dependent manner, the proliferation of T-cells induced by IL-1, IL-2, IL-3, IL-4, IL-6, IL-7, IL-12, and IL-15 as well as by alloantigens and mitogens. The block of T-cells activation occurs through mechanisms including signal transduction both Ca^+ dependent, as in the case of cyclosporine and tacrolimus, and Ca^+ independent. It may be also used together with MMF for a steroid-free immunosuppressive regimen. Sorìa et al.[84] carried out an open prospective study on rapamycin: 7 women with CEOLP applied topical rapamycin (1 mg/mL) on oral erosive lesions twice a day for 3 months. At 3 months, four women had complete remission and two women had partial remission with minimal side effects.

One of the major focus in lichen planus treatment has been the development of biological agents that provide selective immunological results with less side effects than generic immunossupressants. Many topical and systemic targeted immunotherapeutic agents (TIs), also known as biological agents, are currently available for off-label use in OLP, even if an effective treatment modality remains elusive. These molecules are proteins derived from recombinant DNA technology in form of monoclonal antibodies and receptor-antobody fusion proteins which target specific mediators of inflammation. Their use is considered a safer alternative to traditional systemic immunosuppressive agents in treatment of rheumatoid arthritis and related conditions because they block only a specific molecular step of the immune system. Biologics comprise two main groups: (1) agents targeting the cytokine TNF-α (e.g. etanercept, infliximab, adalimumab) and (2) agents targeting T cells or antigen-presenting cells (e.g. efalizumab, alefacept). To date, biologics employment in clinical oral medicine is less commonly discussed and limited to case reports or case series often with a single agent. The rationale for their use in OLP is based on the fact that activated $CD4^+$ lymphocytes play a pivotal role in the pathogenesis of the disease and cytokines such as TNF-α, IL-2, and IFN-γ are involved in the activation and persistence of inflammation in OLP, making it a prototypical Th1 inflammatory pattern. Cheng and Mann[85] reported a case of a 54-year-old woman with erosive OLP resistant

to steroid (prednisone 60 mg/d tapered over 18 days) and topical tacrolimus ointment (twice daily) and treated with efalizumab (Raptiva). It is a humanized monoclonal antibody that binds the CD11a subunit of LFA-1. LFA-1 is a T-cell surface molecule and ICAM-1 is its partner molecule. The interaction between LFA-1 and ICAM-1 regulates many normal T-cell functions. Binding of efalizumab to CD11a on T cells blocks the interaction between LFA-1 and ICAM-1, thus interfering with T-cell activation, migration and cytotoxic functions. This blockade is reversible, does not deplete T cells or cause end-organ toxicity, opportunistic infections or malignancy.[86] Platelet count monitoring is recommend. Cheng[85] reported an improvement of oral and cutaneous lesions at 5 weeks after commencement efalizumab therapy (initial dose of 0.7 mg/kg/week, followed by 1.0 mg/kg per week).

Infliximab (Remicade) is a chimeric (human/mouse) IgG1anti-TNF-α monoclonal antibody. It prevents the binding of TNF-α to its receptor and also fixes complement, inducing antibody-mediated cytotoxicity which results in lysis of cells expressing membrane-bound TNF-α. It is given by intravenous infusion. A standard induction course consists of 5 mg/kg at weeks 0, 2, and 6, followed by single infusions at 8-12-week intervals. It is relatively well-tolerated. During therapy, however, human antichimeric antibodies may develop. These latter may be reduced through a concurrent immunosuppressive therapy or premedication with corticosteroids. Connolly et al.[87] successfully employed infliximab for treatment of orogenital ulcerations in a patient with diagnosis of Behcet'disease. Currently there are no studies published about its employment in OLP treatment.

Another biologic molecule is represented by etanercept (Enbrel) which is a 100% human TNF soluble receptor composed of the extracellular portion of two TNF type II receptors joined to the Fc portion of IgG1. The binding of etanercept to TNF-α renders TNF biologically inactive, thus reducing inflammatory activity. It was the first TNF antagonist approved for treatment of psoriasis and psoriatic arthritis and is administered as subcutaneous injection at a dose which varies depending on the disease that must be treated.[88]

Yarom[89] published a case report of a 56-year-old woman with multiple white mucosal lesions in the oral cavity suggestive for OLP and confirmed by histhopathology and DIF studies. Conventional treatments with corticosteroids, tacrolimus, azathioprine did not provide benefits. Subcutaneus etanercept (25 mg twice weekly) was administered with clinical improvement lesions documented 4 week after beginning therapy. After 10 weeks, the patients suspended the treatment because of its expensive costs. Exacerbation of symptoms was noticed and controlled with steroids. In any case, symptoms relief during the last 3 years was obtained only with systemic corticosteroids and etanercept.

Fivenson et al.[90] reported two cases of generalized lichen planus treated with alefacept (Amevive), a recombinant protein which binds to CD2 on memory-effector T-lymphocytes, inhibiting their activation and reducing their number. It is composed of an LFA-3 protein and human IgG1 fragment crystallizable (Fc) domain. Alefacept is approved for treatment of moderate to severe plaque psoriasis.[91] It can be administred by intramuscular injection or intravenous infusion. The rationale for alefacept use in treatment of lichen planus is that this pathology is $CD4^+$ T-cell mediated and this drug induces T-cells apoptosis through natural-killer cells release of granzyme. The results collected from Fivenson et al.[92] suggest that alefacept is a safe alternative for management of those OLP cases long-standing and recalcitrant to common therapies. Both their patients, in fact, experienced an improvement of lesions without adverse events.

Finally, Rituximab is a chimeric murine-human monoclonal antibody to CD20 (a B-cell specific antigen) which induces depletion of B cells *in vivo*.[92] Its cytotoxicity is mediated by three mechanisms which include antibody-dependent cytotoxicity, complement-mediated lysis, direct disruption of signaling pathways and triggering of apoptosis. It has been used for management of Pemphigus vulgaris (PV), paraneoplastic pemphigus, dermatomiyositis, and GVHD.[93–95] The successful employing of rituximab in management of PV is related to a depletion of B cells resulting in a decrease in production of the disease-causing autoantibodies.[96] This finding would suggest that most of PV autoantibodies are produced by $CD20^+$ B-cell clones susceptible to rituximab. No study of its use on OLP has been carried out.

Conclusions

Although data and clinical experience about biologics are still limited and related to uncontrolled case reports and their long-term toxicity is uncertain, the findings collected are encouraging. It has been shown, in fact, an improvement in symptoms and quality of life in patients with long-standing lesions resistant to common therapies. Potential limitation in the use of these molecules are represented by the high costs of treatments, side effects and lack of long-term follow-up.

Therefore, controlled studies are mandatory to provide more evidence about the use of these new agents in oral medicine. In any case, biologics employment should be confined to patients with severe lesions or those resistant to traditional first- and second-line therapies, such as topical corticosteroids.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Setterfield, J.F., Neill, S., Shirlaw, P.J., Theron, J., Vaughan, R., Escudier, M., Challacombe, S.J., Black, M.M. The vulvovaginal gingival syndrome: a severe subgroup of lichen planus with characteristic clinical features and a novel association with the class II HLA DQB1*0201 allele. J. Am. Acad. Dermatol. 2006, 55, 98–113.
2. Quispel, R., van Boxel, O.S., Schipper, M.E., Sigurdsson, V., Canninga-van Dijk, M.R., Kerckhoffs, A., Smout, A.J., Samsom, M., Schwartz, M.P. High prevalence of esophageal involvement in lichen planus: a study using magnification chromoendoscopy. Endoscopy 2009, 41, 187–193.
3. Thorne, J.E., Jabs, D.A., Nikolskaia, O.V., Mimouni, D., Anhalt, G.J., Nousari, H.C. Lichen planus and cicatrizing conjunctivitis: characterization of five cases. Am. J. Ophthalmol. 2003, 136, 239–243.
4. Mignogna, M.D., Lo Russo, L., Fedele, S. Gingival involvement of oral lichen planus in a series of 700 patients. J. Clin. Periodontol. 2005, 32, 1029–1033.
5. González Moles, M.A., Esteban, F., Ruiz-Avila, I., Gil Montoya, J.A., Brener, S., Bascones-Martínez, A., Muñoz, M. A role for the substance P/NK-1 receptor complex in cell proliferation and apoptosis in oral lichen planus. Oral Dis. 2009, 15, 162–169.
6. Pinholt, E.M., Rindum, J., Pindborg, J.J. Oral cancer: a retrospective study of 100 Danish cases. Br. J. Oral Maxillofac. Surg. 1997, 35, 77–80.
7. Ingafou, M., Leao, J.C., Porter, S.R., Scully, C. Oral lichen planus: a retrospective study of 690 British patients. Oral Dis. 2006, 12, 463–468.
8. Bricker, S.L. Oral lichen planus: a review. Semin. Dermatol. 1994, 13, 87–90.
9. Thorn, J.J., Holmstrup, P., Rindum, J., Pindborg, J.J. Course of various clinical forms of oral lichen planus. A prospective follow-up study of 611 patients. J. Oral Pathol. 1988, 17, 213–218.
10. Ismail, S.B., Kumar, S.K., Zain, R.B. Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis, management and malignant transformation. J. Oral Sci. 2007, 49, 89–106.
11. Al-Hashimi, I., Schifter, M., Lockhart, P.B., Wray, D., Brennan, M., Migliorati, C.A., Axéll, T., Bruce, A.J., Carpenter, W., Eisenberg, E., Epstein, J.B., Holmstrup, P., Jontell, M., Lozada-Nur, F., Nair, R., Silverman, B., Thongprasom, K., Thornhill, M., Warnakulasuriya, S., van der Waal, I. Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 2007, 103 Suppl, S25.e1–S25.12.
12. Thornhill, M.H., Pemberton, M.N., Simmons, R.K., Theaker, E.D. Amalgam-contact hypersensitivity lesions and oral lichen planus. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 2003, 95, 291–299.
13. Carrozzo, M., Thorpe, R. Oral lichen planus: a review. Minerva Stomatol. 2009, 58, 519–537.
14. Walsh, L.J., Savage, N.W., Ishii, T., Seymour, G.J. Immunopathogenesis of oral lichen planus. J. Oral Pathol. Med. 1990, 19, 389–396.
15. Carrozzo, M., Uboldi de Capei, M., Dametto, E., Fasano, M.E., Arduino, P., Broccoletti, R., Vezza, D., Rendine, S., Curtoni, E.S., Gandolfo, S. Tumor necrosis factor-alpha and interferon-gamma polymorphisms contribute to susceptibility to oral lichen planus. J. Invest. Dermatol. 2004, 122, 87–94.
16. Fujita, H., Kobayashi, T., Tai, H., Nagata, M., Hoshina, H., Nishizawa, R., Takagi, R., Yoshie, H. Assessment of 14 functional gene polymorphisms in Japanese patients with oral lichen planus: a pilot case-control study. Int. J. Oral Maxillofac. Surg. 2009, 38, 978–983.
17. Bouma, G., Xia, B., Crusius, J.B., Bioque, G., Koutroubakis, I., Von Blomberg, B.M., Meuwissen, S.G., Peña, A.S. Distribution of four polymorphisms in the tumour necrosis factor (TNF) genes in patients with inflammatory bowel disease (IBD). Clin. Exp. Immunol. 1996, 103, 391–396.
18. Simark-Mattsson, C., Bergenholtz, G., Jontell, M., Eklund, C., Seymour, G.J., Sugerman, P.B., Savage, N.W., Dahlgren, U.I. Distribution of interleukin-2, -4, -10, tumour necrosis factor-alpha and transforming growth factor-beta mRNAs in oral lichen planus. Arch. Oral Biol. 1999, 44, 499–507.
19. Carrozzo, M. Oral diseases associated with hepatitis C virus infection. Part 2: lichen planus and other diseases. Oral Dis. 2008, 14, 217–228.
20. Carrozzo, M., Brancatello, F., Dametto, E., Arduino, P., Pentenero, M., Rendine, S., Porter, S.R., Lodi, G., Scully, C., Gandolfo, S. Hepatitis C virus-associated oral lichen planus: is the geographical heterogeneity related to HLA-DR6? J. Oral Pathol. Med. 2005, 34, 204–208.
21. Wenzel, J., Scheler, M., Proelss, J., Bieber, T., Tüting, T. Type I interferon-associated cytotoxic inflammation in lichen planus. J. Cutan. Pathol. 2006, 33, 672–678.
22. Rice, P.J., Hamburger, J. Oral lichenoid drug eruptions: their recognition and management. Dent. Update 2002, 29, 442–447.
23. van der Meij, E.H., 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, 507–512.
24. van der Waal, I. Oral lichen planus and oral lichenoid lesions; a critical appraisal with emphasis on the diagnostic aspects.Med Oral Patol Oral Cir Bucal, 2009, 14, 310–314.
25. Eisenberg, E. Clinicopathologic patterns of oral lichenoid lesions. Oral Maxillofac Surg Clin North Am, 1994, 6, 445.
26. Mutasim, D.F., Adams, B.B. Immunofluorescence in dermatology. J. Am. Acad. Dermatol. 2001, 45, 803–22; quiz 822.
27. Helander, S.D., Rogers, R.S. 3rd. The sensitivity and specificity of direct immunofluorescence testing in disorders of mucous membranes. J. Am. Acad. Dermatol. 1994, 30, 65–75.
28. Kanokvalai, K, Sukhum, J., Supenya, V., Pinkaew S., Sutthipinittharm P. Direct immunofluorescence study in patients with lichen planus. Int J Dermatol, 2007, 46, 1237–1241.
29. Camisa, C., Neff, J.C., Olsen, R.G. Use of indirect immunofluorescence in the lupus erythematosus/lichen planus overlap syndrome: an additional diagnostic clue. J. Am. Acad. Dermatol. 1984, 11, 1050–1059.
30. Inaloz, H.S., Chowdhury, M.M.U., Motley, R.J. Scarring alopecia in LE/LP overlap syndrome: a case report. J Eur Acad Dermatol Venereol, 2000, 15, 171–174.
31. Rhodus, N.L., Cheng, B., Ondrey, F. Th1/Th2 cytokine ratio in tissue transudates from patients with oral lichen planus. Mediators Inflamm. 2007, 2007, 19854.
32. Krutchkoff, D.J., Cutler, L., Laskowski, S. Oral lichen planus: the evidence regarding potential malignant transformation. J. Oral Pathol. 1978, 7, 1–7.
33. van der Meij, E.H., 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, 164–171.
34. Gandolfo, S., Richiardi, L., Carrozzo, M., Broccoletti, R., Carbone, M., Pagano, M., Vestita, C., Rosso, S., Merletti, F. Risk of oral squamous cell carcinoma in 402 patients with oral lichen planus: a follow-up study in an Italian population. Oral Oncol. 2004, 40, 77–83.
35. Lanfranchi-Tizeira, H.E., Aguas, S.C., Sano, S.M. Malignant transformation of atypical oral lichen planus: a review of 32 cases. Med. Oral 2003, 8, 2–9.
36. Mignogna, M.D., Lo Muzio, L., Lo Russo, L., 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, 262–267.
37. Lozada-Nur, F. Oral lichen planus and oral cancer: is there enough epidemiologic evidence? Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 2000, 89, 265–266.
38. Fatahzadeh, M., Rinaggio, J., Chiodo, T. Squamous cell carcinoma arising in an oral lichenoid lesion. J. Am. Dent. Assoc. 2004, 135, 754–9; quiz 796.

39. Lo Muzio, L., Mignogna, M.D., Favia, G., Procaccini, M., Testa, N.F., Bucci, E. The possible association between oral lichen planus and oral squamous cell carcinoma: a clinical evaluation on 14 cases and a review of the literature. Oral Oncol. 1998, 34, 239–246.
40. Mignogna, M.D., Lo Russo, L., Fedele, S., Ruoppo, E., Califano, L., Lo Muzio, L. Clinical behaviour of malignant transforming oral lichen planus. Eur. J. Surg. Oncol. 2002, 28, 838–843.
41. Markopoulos, A.K., Antoniades, D., Papanayotou, P., Trigonidis, G. Malignant potential of oral lichen planus; a follow-up study of 326 patients. Oral Oncol. 1997, 33, 263–269.
42. Mignogna, M.D., Fedele, S., Lo Russo, L., Mignogna, C., de Rosa, G., Porter, S.R. Field cancerization in oral lichen planus. Eur. J. Surg. Oncol. 2007, 33, 383–389.
43. van der Meij, E.H., Mast, H., van der Waal, I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective five-year follow-up study of 192 patients. Oral Oncol. 2007, 43, 742–748.
44. Mattsson, U., Jontell, M., Holmstrup, P. Oral lichen planus and malignant transformation: is a recall of patients justified? Crit. Rev. Oral Biol. Med. 2002, 13, 390–396.
45. Scully, C., Beyli, M., Ferreiro, M.C., Ficarra, G., Gill, Y., Griffiths, M., Holmstrup, P., Mutlu, S., Porter, S., Wray, D. Update on oral lichen planus: etiopathogenesis and management. Crit. Rev. Oral Biol. Med. 1998, 9, 86–122.
46. Scully, C., Eisen, D., Carrozzo, M. Management of oral lichen planus. Am. J. Clin. Dermatol. 2000, 1, 287–306.
47. Thomson, M.A., Hamburger, J., Stewart, D.G., Lewis, H.M. Treatment of erosive oral lichen planus with topical tacrolimus. J. Dermatolog. Treat. 2004, 15, 308–314.
48. Byrd, J.A., Davis, M.D., Bruce, A.J., Drage, L.A., Rogers, R.S. 3rd. Response of oral lichen planus to topical tacrolimus in 37 patients. Arch. Dermatol. 2004, 140, 1508–1512.
49. Branchet, M.C., Boisnic, S., Pascal, F., Ben Slama, L., Rostin, M., Szpirglas, H. [Topical tretinoin in the treatment of lichen planus and leukoplakia of the oral mucosa. A biochemical evaluation of the keratinization]. Ann. Dermatol. Venereol. 1994, 121, 464–469.
50. Eisen, D. Hydroxychloroquine sulfate (Plaquenil) improves oral lichen planus: An open trial. J. Am. Acad. Dermatol. 1993, 28, 609–612.
51. Setterfield, J.F., Black, M.M., Challacombe, S.J. The management of oral lichen planus. Clin. Exp. Dermatol. 2000, 25, 176–182.
52. Plemons, J.M., Rees, T.D., Zachariah, N.Y. Absorption of a topical steroid and evaluation of adrenal suppression in patients with erosive lichen planus. Oral Surg. Oral Med. Oral Pathol. 1990, 69, 688–693.
53. Vincent, S.D., Fotos, P.G., Baker, K.A., Williams, T.P. Oral lichen planus: the clinical, historical, and therapeutic features of 100 cases. Oral Surg. Oral Med. Oral Pathol. 1990, 70, 165–171.
54. Lozada-Nur, F., Huang, M.Z., Zhou, G.A. Open preliminary clinical trial of clobetasol propionate ointment in adhesive paste for treatment of chronic oral vesiculoerosive diseases. Oral Surg. Oral Med. Oral Pathol. 1991, 71, 283–287.
55. Mollaoglu, N. Oral lichen planus: a review. Br. J. Oral Maxillofac. Surg. 2000, 38, 370–377.
56. Silverman, S. Jr, 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, 665–670.
57. Eisen, D. The therapy of oral lichen planus. Crit. Rev. Oral Biol. Med. 1993, 4, 141–158.
58. Boisnic, S., Licu, D., Ben Slama, L., Branchet-Gumila, M.C., Szpirglas, H., Dupuy, P. Topical retinaldehyde treatment in oral lichen planus and leukoplakia. Int. J. Tissue React. 2002, 24, 123–130.
59. 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, 21–25.
60. Eisen, D., Ellis, C.N., Duell, E.A., Griffiths, C.E., Voorhees, J.J. Effect of topical cyclosporine rinse on oral lichen planus. A double-blind analysis. N. Engl. J. Med. 1990, 323, 290–294.
61. Bécherel, P.A., Chosidow, O., Boisnic, S., Moyal-Barraco, M., Pelisse, M., Reigneau, O., Francès, C. Topical cyclosporine in the treatment of oral and vulvar erosive lichen planus: a blood level monitoring study. Arch. Dermatol. 1995, 131, 495–496.
62. Sieg, P., Von Domarus, H., Von Zitzewitz, V., Iven, H., Färber, L. Topical cyclosporin in oral lichen planus: a controlled, randomized, prospective trial. Br. J. Dermatol. 1995, 132, 790–794.
63. Ruzicka, T., Assmann, T., Homey, B. Tacrolimus: the drug for the turn of the millennium? Arch. Dermatol. 1999, 135, 574–580.
64. Böhm, M., Beissert, S., Schwarz, T., Metze, D., Luger, T. Bullous pemphigoid treated with mycophenolate mofetil. Lancet 1997, 349, 541.
65. Grundmann-Kollmann, M., Podda, M., Ochsendorf, F., Boehncke, W.H., Kaufmann, R., Zollner, T.M. Mycophenolate mofetil is effective in the treatment of atopic dermatitis. Arch. Dermatol. 2001, 137, 870–873.
66. Basara, N., Blau, W.I., Kiehl, M.G., Römer, E., Rudolphi, M., Bischoff, M., Kirsten, D., Sanchez, H., Günzelmann, S., Fauser, A.A. Efficacy and safety of mycophenolate mofetil for the treatment of acute and chronic GVHD in bone marrow transplant recipient. Transplant. Proc. 1998, 30, 4087–4089.
67. Nousari, H.C., Goyal, S., Anhalt, G.J. Successful treatment of resistant hypertrophic and bullous lichen planus with mycophenolate mofetil. Arch. Dermatol. 1999, 135, 1420–1421.
68. Frieling, U., Bonsmann, G., Schwarz, T., Luger, T.A., Beissert, S. Treatment of severe lichen planus with mycophenolate mofetil. J. Am. Acad. Dermatol. 2003, 49, 1063–1066.
69. Nylander Lundqvist, E., Wahlin, Y.B., Hofer, P.A. Methotrexate supplemented with steroid ointments for the treatment of severe erosive lichen ruber. Acta Derm. Venereol. 2002, 82, 63–64.
70. Rozycki, T.W., Rogers, R.S. 3rd, Pittelkow, M.R., McEvoy, M.T., el-Azhary, R.A., Bruce, A.J., Fiore, J.P., Davis, M.D. Topical tacrolimus in the treatment of symptomatic oral lichen planus: a series of 13 patients. J. Am. Acad. Dermatol. 2002, 46, 27–34.
71. Ruzicka, T., Bieber, T., Schöpf, E., Rubins, A., Dobozy, A., Bos, J.D., Jablonska, S., Ahmed, I., Thestrup-Pedersen, K., Daniel, F., Finzi, A., Reitamo, S. A short-term trial of tacrolimus ointment for atopic dermatitis. European Tacrolimus Multicenter Atopic Dermatitis Study Group. N. Engl. J. Med. 1997, 337, 816–821.
72. Fung, J.J., Todo, S., Tzakis, A., Demetris, A., Jain, A., Abu-Elmaged, K., Alessiani, M., Starzl, T.E. Conversion of liver allograft recipients from cyclosporine to FK 506-based immunosuppression: benefits and pitfalls. Transplant. Proc. 1991, 23, 14–21.
73. Kelly, P.A., Burckart, G.J., Venkataramanan, R. Tacrolimus: a new immunosuppressive agent. Am. J. Health. Syst. Pharm. 1995, 52, 1521–1535.
74. Meingassner, J.G., Stütz, A. Immunosuppressive macrolides of the type FK 506: a novel class of topical agents for treatment of skin diseases? J. Invest. Dermatol. 1992, 98, 851–855.
75. Aoyama, H., Tabata, N., Tanaka, M., Uesugi, Y., Tagami, H. Successful treatment of resistant facial lesions of atopic dermatitis with 0.1% FK506 ointment. Br. J. Dermatol. 1995, 133, 494–496.
76. Vente, C., Reich, K., Rupprecht, R., Neumann, C. Erosive mucosal lichen planus: response to topical treatment with tacrolimus. Br. J. Dermatol. 1999, 140, 338–342.
77. Reich, K., Vente, C., Neumann, C. Topical tacrolimus for pyoderma gangrenosum. Br. J. Dermatol. 1998, 139, 755–757.
78. Kaliakatsou, F., Hodgson, T.A., Lewsey, J.D., Hegarty, A.M., Murphy, A.G., Porter, S.R. Management of recalcitrant ulcerative oral lichen planus with topical tacrolimus. J. Am. Acad. Dermatol. 2002, 46, 35–41.
79. US Food and Drug Administration: FDA Public Health Advisory: Elidel (pimecrolimus) cream and Protopic (tacrolimus) ointment. 3-10-2005.
80. Becker, J.C., Houben, R., Vetter, C.S., Bröcker, E.B. The carcinogenic potential of tacrolimus ointment beyond immune suppression: a hypothesis creating case report. BMC Cancer 2006, 6, 7.
81. Swift, J.C., Rees, T.D., Plemons, J.M., Hallmon, W.W., Wright, J.C. The effectiveness of 1% pimecrolimus cream in the treatment of oral erosive lichen planus. J. Periodontol. 2005, 76, 627–635.

82. Passeron, T., Lacour, J.P., Fontas, E., Ortonne, J.P. Treatment of oral erosive lichen planus with 1% pimecrolimus cream: a double-blind, randomized, prospective trial with measurement of pimecrolimus levels in the blood. Arch. Dermatol. 2007, 143, 472–476.
83. Volz, T., Caroli, U., Lüdtke, H., Bräutigam, M., Kohler-Späth, H., Röcken, M., Biedermann, T. Pimecrolimus cream 1% in erosive oral lichen planus–a prospective randomized double-blind vehicle-controlled study. Br. J. Dermatol. 2008, 159, 936–941.
84. Soria, A., Agbo-Godeau, S., Taïeb, A., Francès, C. Treatment of refractory oral erosive lichen planus with topical rapamycin: 7 cases. Dermatology (Basel). 2009, 218, 22–25.
85. Cheng, A., Mann, C. Oral erosive lichen planus treated with efalizumab. Arch. Dermatol. 2006, 142, 680–682.
86. Gottlieb, A.B., Gordon, K.B., Hamilton, T.K. Maintenance of efficacy and safety with continuous efalizumab therapy in patients with moderate to severe chronic plaque psoriasis: final phase IIIb study results. Poster presented at the 63rd Annual Meeting of the American Academy of Dermatology; February 18-22, 2005, New Orleans, La.
87. Connolly, M., Armstrong, J.S., Buckley, D.A. Infliximab treatment for severe orogenital ulceration in Behçet's disease. Br. J. Dermatol. 2005, 153, 1073–1075.
88. Spencer-Green G. Etanercept (Enbrel): update on therapeutic use. Ann Rheum Dis, 2000, 59 Suppl 1, 146–149.
89. Yarom, N. Etanercept for the management of oral lichen planus. Am. J. Clin. Dermatol. 2007, 8, 121.
90. Fivenson, D.P., Mathes, B. Treatment of generalized lichen planus with alefacept. Arch. Dermatol. 2006, 142, 151–152.
91. Chamian, F., Lin, S.L., Lee, E., Kikuchi, T., Gilleaudeau, P., Sullivan-Whalen, M., Cardinale, I., Khatcherian, A., Novitskaya, I., Wittkowski, K.M., Krueger, J.G., Lowes, M.A. Alefacept (anti-CD2) causes a selective reduction in circulating effector memory T cells (Tem) and relative preservation of central memory T cells (Tcm) in psoriasis. J Transl Med, 2007, 7, 5–27.
92. Grillo-López, A.J. Rituximab: an insider's historical perspective. Semin. Oncol. 2000, 27, 9–16.
93. Cooper, H.L., Healy, E., Theaker, J.M., Friedmann, P.S. Treatment of resistant pemphigus vulgaris with an anti-CD20 monoclonal antibody (Rituximab). Clin. Exp. Dermatol. 2003, 28, 366–368.
94. Barnadas, M., Roe, E., Brunet, S., Garcia, P., Bergua, P., Pimentel, L., Puig, L., Francia, A., García, R., Gelpí, C., Sierra, J., Coll, P., Alomar, A. Therapy of paraneoplastic pemphigus with Rituximab: a case report and review of literature. J. Eur. Acad. Dermatol. Venereol. 2006, 20, 69–74.
95. Cutler, C., Miklos, D., Kim, H.T., Treister, N., Woo, S.B., Bienfang, D., Klickstein, L.B., Levin, J., Miller, K., Reynolds, C., Macdonell, R., Pasek, M., Lee, S.J., Ho, V., Soiffer, R., Antin, J.H., Ritz, J., Alyea, E. Rituximab for steroid-refractory chronic graft-versus-host disease. Blood 2006, 108, 756–762.
96. Salopek, T.G., Logsetty, S., Tredget, E.E. Anti-CD20 chimeric monoclonal antibody (rituximab) for the treatment of recalcitrant, life-threatening pemphigus vulgaris with implications in the pathogenesis of the disorder. J. Am. Acad. Dermatol. 2002, 47, 785–788.