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Topical Retinoids in Oral Lichen Planus Treatment: An Overview

Massimo Petruzzi[a] Alberta Lucchese[b] Carlo Lajolo[c] Guglielmo Campus[d]
Dorina Lauritano[e] Rosario Serpico[b]

[a]Dental Clinic, Faculty of Medicine and Surgery, University 'Aldo Moro', Bari, [b]Dental School, Second University of Naples, Naples, [c]Dental Section, Catholic University 'Sacro Cuore', Rome, [d]Dental Institute, University of Sassari, Sassari, and [e]Dental Institute, University of Milano-Bicocca, Milano, Italy

Key Words
Oral lichen · Retinoids · Treatment · Topical

Abstract
Background: Treatment of oral lichen planus (OLP) is a major challenge for clinicians and patients. There is limited scientific evidence about topical treatment with retinoids. We conducted a literature review of data on the effectiveness and safety of topical retinoids in OLP patients. ***Materials and Methods:*** We searched the MEDLINE, Embase and Cochrane databases for articles on topical retinoids treatment on OLP patients (searches from 1970 to February 2012). ***Results:*** Sixteen studies (280 OLP patients topically treated with different classes of retinoids) met the inclusion criteria. Isotretinoin was the most frequently employed retinoid in the treatment of OLP. The clinical and/or histopathological efficacy of retinoids was recorded in the majority of the selected studies. A transient and moderate burning sensation was the most frequently reported side effect. ***Conclusions:*** Topical retinoids appear as an alternative choice in OLP treatment. Whether keratotic OLP better responds to topical retinoids than erosive OLP is still an open question that deserves further comparative and controlled clinical trials. The benefits and harms of using topical retinoids in people with OLP require thorough evaluation in properly designed controlled studies.

Introduction

Oral lichen planus (OLP) is a chronic autoimmune mucosal disease characterized by abnormalities in the growth and differentiation of basal keratinocytes whose surface antigens are modified because of primary autoimmune damage. The autoimmune insult leads to a delay in the growth of mucosal epithelium which is responsible for hyperkeratosis and acanthosis [1, 2]. The T cellular infiltrate which is present in the corium bears evidence that the cellular inflammatory component is important in maintaining the process of OLP.

Retinoids are a family of polyisoprenoid lipids derived from vitamin A (retinol) and its natural and synthetic analogs. Based on the structural features and reflecting the time of introduction, retinoids can be classified into four different generations: the first generation includes retinol, tretinoin, isotretinoin, retinal, and alitretinoin, the second generation includes etretinate and its metabolite acitretin, the third generation includes tazarotene, bexarotene and adapalene, and the fourth generation that includes Seletinoid G [3, 4]. Specific nuclear receptors (RAR-α, RAR-β, RAR-γ and RXR-α, RXR-β, RXR-γ) bind their retinoid ligands, target to DNA response sites upstream of retinoid responsive genes, and up-/downregulate transcription [5]. Thanks to this signaling pathway, retinoids can regulate epithelial cell growth and differentiation and activate genes that can suppress tumorigenesis [6]. They also have a modulating function on inflammatory and immunocompetent cells, including T cells and macrophages [7]. These pharmacological effects are used in different dermatological pathologies such as acne vulgaris, psoriasis, actinic keratosis and rosacea [8]. Topical retinoids are drugs marketed for skin use and their use on oral mucosa presents some problems. In fact, in the oral cavity, it is impossible to perform an occlusive treatment as saliva quickly removes the applied cream or ointment. Retinoids are used as off-label drugs in some oral pathologies (leukoplakia and OLP) and a mucosal adhesive paste (Orabase) is added to enhance their adherence on the oral mucosa [9].

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E-Mail karger@karger.com
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Massimo Petruzzi, DDS, PhD
Clinica Odontoiatrica, Policlinico di Bari
Piazza Giulio Cesare 11
IT–70124 Bari (Italy)
E-Mail massimo.petruzzi@uniba.it

Oral mucosal lesions related to OLP can benefit from systemic and/or topical retinoids administration, but to date there are no specific and detailed guidelines on the benefits and harms of topical retinoids in patients with OLP. Reports of treatment with topical retinoids in OLP are limited and in most cases restricted to small case series. We performed a literature review and critical appraisal of the existing literature on the benefits and harms of topical retinoids in people with OLP.

Materials and Methods

We searched the MEDLINE, Embase and Cochrane databases (1970 to February 2012) for clinical trials on OLP treatment with topical retinoids. In the absence of clinical trials, fewer incidences were identified, including cohort studies, case reports and case series. The key words 'oral lichen and retinoid' and 'oral lichen and vitamin A' were used to search databases. The search was limited to English language studies conducted in humans. Studies were eligible only if the treatment described was topical. We excluded reviews and studies of extra-oral localization of lichen and studies in which retinoids were administered exclusively systemically. Reference lists of all retrieved articles were screened for additional studies that might be potentially eligible for meeting the inclusion criteria. If any were identified, these were included in our analysis.

Data on the characteristics of the study population, intervention and outcome measures were extracted. Extraction of data was for type of study, number of patients treated, patients' gender and age, OLP clinical type and mean duration, type of retinoid employed, modality of administration, follow-up duration, side effects, percentage of OLP lesions or patients healed and/or improved and main conclusions.

Results

Our search identified 85 citations for 'oral lichen and retinoid' and 43 citations for 'oral lichen and vitamin A'. Sixteen studies met the inclusion criteria [10–25] and their characteristics are detailed in table 1.

There were one single case report [22], three case series [10, 13, 17], three observational studies [14, 20, 24] and nine controlled clinical trials [11, 12, 15, 16, 18, 19, 21, 23, 25]. A total of 264 patients were described in these 16 studies: 84 were men, 132 were women (for 48 patients sex was not reported), mean age was 49.7 years. Mean duration of OLP signs and symptoms was 3.3 years (data from 9 studies) [11–13, 15, 18–20, 22, 25]; there were no data on duration of OLP in the remaining studies. Seven studies [10, 13, 16, 17, 20–22] only considered patients affected by reticular OLP, two studies only considered erosive OLP patients [12, 19], five studies studied reticular and erosive OLP patients [11, 15, 18, 23, 25] and in the remaining two studies the OLP clinical form was not specified. Table 2 reports detailed information about the retinoids employed in the included studies.

Retinoic acid 0.1% was administered in two studies [10, 13], tretinoin at different concentrations (0.05, 0.1, 0.2 and 0.3%) was employed in six studies [11, 12, 16, 18, 19, 22] and in one of this it was associated to a class II topical corticosteroid (unspecified) [22]. Five studies [14, 15, 23–25] evaluated the efficacy of topical isotretinoin (0.05, 0.1 and 0.18%) while only single studies were conducted on topical fenretinide, retinaldehyde and tazarotene in OLP patients [17, 20, 21]. The mean duration of topical treatment was 2.3 months and patients applied the retinoids on average of 2.3 times/day.

In nine studies there was no follow-up period: the described results were reported immediately following treatment [14–21, 24]. Only three studies were planned with an adequate follow-up period [22, 23, 25]. The remaining studies reported on a follow-up period of few months or weeks.

Seven studies of the sixteen included reported about side effects: burning sensation (mostly transient) was the most common, but also soreness, scaling of the lip, desquamation, erythema and taste disturbance were recorded as consequential to topical retinoids application [10, 11, 15, 18, 20, 21, 23]. In five studies [12, 14, 17, 19, 25] the authors did not observe side effects while in the remaining four studies, the authors did not evaluate the side effect. A mean of 73% of improvement (or healing) of OLP lesions or patients was calculated considering only the studies that reported the percentage of amelioration or healing [10–13, 15, 17–23, 25].

Discussion

A recent Cochrane review concluded that 'there is insufficient evidence to support the effectiveness of any specific treatment in the course of OLP' [26]. To date, potent topical corticosteroids are considered the first-line treatment for symptomatic OLP at any site, however their therapeutic benefit in terms of signs and symptoms remission is not always evident. Some patients (the so-called 'resistant subjects') do not respond adequately to the treatment or are allergic or insensitive to topical glucocorticoids [27]. Moreover, prolonged use of topical corticosteroids may result in drug tolerance or secondary candidiasis [28, 29]. Topical retinoids (creams, lotions and gels containing one or other group of medicines derived from vitamin A) could represent an adequate alternative to topical corticosteroids. In fact, since the early 1970s, different studies have reported on topical application of retinoids in OLP patients.

Günther [10] first reported on vitamin A acid 0.1% (retinoic acid) administered topically and/or systemically in 17 OLP patients. Daily dosage, duration of topical treatment and how topical and systemic treatment was combined was not specified. The author reported that topical applications of retinoic acid reduced the size of OLP lesions within 3 weeks. This period probably correspond to the time required for the renewal of the epithelium. The relapse corresponds to an absence of changes of metabolism in the cells, perturbed in the lichen planus after treatment by retinoids.

These preliminary results were confirmed by Sloberg et al. [11] who treated 23 OLP patients with topical tretinoin 0.1%, comparing the efficacy with a placebo group. They noted a statistically significant amelioration of OLP lesions in treated patients with minimal local side effects. However, they pointed out the high incidence of lesion recurrence after treatment cessation. The same researchers, 4 years later, analyzed a cohort of 25 OLP patients previously treated with systemic etretinate [12]. The 16 patients who showed a marked improvement were randomly treated with etretinate (low dosage) or topical 0.1% tretinoin (only 9 patients) for 4 months (maintenance period). The authors noted that the topical tretinoin markedly reduced the problems related to systemic administration of retinoids.

Table 1. Patients demographics and OLP clinical characteristics

Reference	Type of study	Treated patients	Gender	Age, years	Mean OLP duration, years	OLP clinical type
Günther, 1973 [10]	case series	17	10 men 7 women	40	not reported	keratotic (4 papular, 5 reticular, 8 plaque)
Sloberg et al., 1979 [11]	controlled clinical trial	23	7 men 16 women	56	5	keratotic (reticular and plaque: 19 lesions) and erosive (17 lesions)
Sloberg et al., 1983 [12]	controlled clinical trial	9	not reported	58	2.5	keratotic (reticular and plaque: 7 lesions) and erosive (9 lesions)
Zegarelli, 1984 [13]	case series	7	4 men 3 women	59	8.5	keratotic (plaque and reticular; lesion and/or patient number not specified)
Regezi et al., 1986 [14]	observational study	20	not reported	not reported	not reported	not reported
Giustina et al., 1986 [15]	controlled clinical trial	22	11 men 11 women	55	6	keratotic and erosive (lesion and/or patient number not specified)
Baudet-Pommel et al., 1991 [16]	controlled clinical trial	10	2 men 8 women	49.7	not reported	keratotic (reticular and plaque lesions; lesion and/or patient number not specified)
Tradati et al., 1994 [17]	case series	2	not reported	not reported	not reported	keratotic (type not specified)
Kar et al., 1996 [18]	controlled clinical trial	16	not reported	42	1.4	keratotic and erosive (lesion and/or patient number not specified)
Buajeeb et al., 1997 [19]	controlled clinical trial	15	2 men 13 women	46	2	erosive
Boisnic et al., 2002 [20]	observational study	16	not reported	57	2	keratotic (plaque and reticular; lesion and/or patient number not specified)
Petruzzi et al., 2002 [21]	controlled clinical trial	6	2 men 4 women	59.3	not reported	keratotic (plaque and reticular; lesion and/or patient number not specified)
Laeijendecker et al., 2005 [22]	case report	1	1 woman	14	1	keratotic (reticular)
Scardina et al., 2006 [23]	controlled clinical trial	70	30 men 40 women	57.8	not reported	keratotic (10 patients with reticular lesions) and erosive (60 patients with atrophic-erosive lesions)
Mastrangelo et al., 2007 [24]	observational study	10	not reported	not reported	not reported	not reported
Piattelli et al., 2007 [25]	controlled clinical trial	20	10 men 10 women	52	0.9	keratotic (10 patients with reticular OLP, 6 patients with plaque OLP) and erosive (4 patients)
Total studies = 16	1 case report 3 case series 3 observational studies 9 controlled clinical trials	264	84 men 132 women 48 not reported	mean: 49.7	mean: 3.3	

Zegarelli [13] reported on 7 cases of reticular OLP treated with vitamin A acid 0.1%. He evidenced a rapid resolution of the treated mucosal areas but at the same time a rapid recurrence of the lesions after treatment was stopped.

Regezi et al. [14] described the histological changes observed in 6 biopsy specimens of OLP patients treated for 2 months with isotretinoin 0.1%. They demonstrated a histopathological amelioration in terms of keratin thickness, basal cells and basement membrane zone preservation and lymphophagocytic infiltrate. The immunostaining for S-100 and HLA-DR indicated a reduction of Langerhans cells and immunocompetent cells in the OLP biopsy specimens.

Giustina et al. [15], in their controlled clinical trial, documented the efficacy of

Table 2. Retinoid treatment characteristics and main outcomes

Reference	Retinoid employed	Administration	Follow-up	Side effects	Improvement or healing (%) and main conclusions
Günther, 1973 [10]	vitamin A acid 0.1% (retinoic acid 0.1%)	alone or in association with systemic vitamin A	2 months	inflammation and occasionally maceration of the treated areas	100% of lesion improvement. Side effects were due to the concomitant systemic treatment. Lesion relapse after withdrawal of retinoic acid.
Sloberg et al., 1979 [11]	tretinoin 0.1%	four times daily for 2 months	3 months	slight redness and scaling of the lip (2 cases), transient soreness	74% of the keratotic lesions improved. 71% of the erosive lesions improved. The frequency of relapses after cessation of treatment was 39%. Tretinoin 0.1% was better than placebo in OLP management.
Sloberg et al., 1983 [12]	tretinoin 0.1%	twice a day for 4 months	4 months	no side effects	0% of lesion improvement. Tretinoin is to be preferred in maintenance treatment of OLP patients previously treated with systemic etretinate.
Zegarelli, 1984 [13]	vitamin A acid 0.1% (retinoic acid 0.1%)	twice a day for 2 weeks	3 weeks (mean)	not reported	90% of OLP lesions disappeared during the treatment. Rapid recurrence after cessation of topical treatment.
Regezi et al., 1986 [14]	isotretinoin 0.1%	twice a day for 2 months	no follow-up	no side effects	After treatment, histological data showed reduction in keratinization, reduction of Langerhans cells, reduced expression of S-100 and HLA-DR of Langerhans cells and dispersion of lymphocytic infiltrate.
Giustina et al., 1986 [15]	isotretinoin 0.1%	twice a day for 2 months	no follow-up	transient burning, superficial desquamation and erythema	90% of OLP lesions disappeared during the treatment. Statistically significant improvement of signs and symptoms. Isotretinoin 0.1% was more efficacious than placebo.
Baudet-Pommel et al., 1991 [16]	tretinoin 0.1%, 0.2% and 0.3%	for 3 months	no follow-up	not reported	No histological differences were noted in patients who received topical tretinoin or systemic etretinate. Distribution and phenotype of inflammatory cells remained similar in the two groups.
Tradati et al., 1994 [17]	fenretinide	100 mg twice a day for 2 months	no follow-up	no side effects	100% of lesion regression. Complete disappearance of local pain and burning sensation.
Kar et al., 1996 [18]	tretinoin 0.05%	twice a day for 2 months	no follow-up	transient burning sensation (3 cases), excessive burning sensation (1 case)	87% of patients reported symptoms improvement. The improvement of signs and symptoms observed in the patients applying tretinoin 0.05% was significantly greater than that in patients applying betamethasone 0.05%.
Buajeeb et al., 1997 [19]	tretinoin 0.05%	four times a day for 1 month	no follow-up	no side effects	46% of patients reported lesion improvement. Fluocinolone acetonide was statistically more efficacious than retinoic acid in erosive OLP.
Boisnic et al., 2002 [20]	retinaldehyde 0.1%	twice a day for 2 months	no follow-up	moderate erythema or burning sensation (8 cases)	88% of patients reported amelioration. 1 patient showed complete OLP disappearance, 13 patients showed improvement while the remaining 2 did not show any amelioration. Reduction in ortho-parakeratosis and downregulation of filaggrin and CK-10 (immunohistochemical data).
Petruzzi et al., 2002 [21]	tazarotene 0.1%	twice a day for 2 months	no follow-up	transient burning sensation and transient taste disturbance	100% of lesion regression or improvement. 4 patients showed complete OLP remission, 2 patients partial remission. Tazarotene was significantly more efficacious than placebo in signs and symptoms management.

Table 2 (continued)

Reference	Retinoid employed	Administration	Follow-up	Side effects	Improvement or healing (%) and main conclusions
Laeijendecker et al., 2005 [22]	tretinoin 0.05% + topical corticosteroid (class II)	for 3 months	2 years	not reported	Complete resolution (100%) of OLP lesions in the pediatric patient.
Scardina et al., 2006 [23]	isotretinoin 0.05% and 0.18%	twice a day for 3 months	10 years	transitory increase in soreness and pain, sensitivity to hot foods	45% of atrophic-erosive OLP improved. 0% of reticular OLP improved. Histopathological and clinical ameliorations noted in the patients receiving isotretinoin 0.18% was statistically significantly better than that in the patients receiving isotretinoin 0.05%. None of the 70 cases showed malignant evolution of OLP lesions.
Mastrangelo et al., 2007 [24]	isotretinoin 0.1%	twice a day for 2 months	no follow-up	not reported	Improvement of the general clinical situation and of the symptomatology. The SEM analysis revealed a regularization of the morphostructural aspect of the oral mucosa.
Piattelli et al., 2007 [25]	isotretinoin 0.1%	three times a day for 4 months	3 years	no side effects	100% of patients had improvement or healing of OLP lesions. The treatment enhances Ki-67 and bcl-2 expression.

isotretinoin 0.1% gel in the treatment of reticular and erosive OLP lesions. Also the placebo group, when starting to apply isotretinoin, showed a significant reduction in lesions and symptoms. As Sloberg, the authors noted a relapse of the disease after stopping the isotretinoin application.

Baudet-Pommel et al. [16] compared the immunopathological changes related to systemic etretinate and topical tretinoin treatment in a cohort of 25 OLP patients (5 were the control group). They noted no difference between the two treated groups in term of CD20+, CD8+ and macrophages. However, the OLP patients who received the retinoids treatment had a shorter evolution of the disease.

In 1994, a study by Tradati et al. [17] evaluated topical fenretinide application in patients with oral leukoplakia and OLP (100 mg b.i.d. for 2 months). Although the method of topical application lacked a controlled drug delivery system (patients broke open and applied the contents of 100 mg capsules), this study demonstrated in the two OLP patients a clinical regression of OLP lesions, no adverse side effects and minimal drug levels in serum. Despite the positive outcome of this small pilot study, additional local fenretinide studies were not conducted.

Kar et al. [18] first reported on a comparative trial between 0.05% tretinoin and 0.05% betamethasone dipropionate applied topically. The improvement observed in the patients applying tretinoin was significantly greater than in those applying betamethasone. The improvement was quicker in reticular and plaque lesions as compared to erosive and atrophic OLP type. The reported side effect was a transient burning sensation after application of tretinoin.

Also Buajeeb et al. [19] compared the efficacy of retinoic acid in Orabase 0.05% with fluocinolone acetonide in Orabase 0.1% in the treatment of atrophic and erosive OLP. Their results suggested that 0.1% fluocinolone acetonide was more efficacious than retinoic acid in OLP signs and symptoms management.

Boisnic et al. [20] studied the clinical, histological and immunohistochemical effects of retinaldehyde, a natural precursor of retinoic acid, on 16 OLP patients. They noted a satisfactory clinical efficacy on 88% of treated patients associated with the improvement or disappearance of histological signs of keratinization defects. Immunohistochemical data revealed downregulation of the expression of keratinization markers as filaggrin and CK-10.

Tazarotene, a third-generation retinoid, was compared by Petruzzi et al. [21] with a placebo in the treatment of reticular OLP. Tazarotene 0.1% resulted more efficacious than placebo in OLP signs and symptoms management, but slight burning sensation and taste abnormalities were recorded as transitory side effects. The authors in conclusion suggested the use of tazarotene in cases of reticular OLP.

Laeijendecker et al. [22] described a case series of three pediatric patients affected by OLP; one patient was treated with topical tretinoin 0.05% in association to topical corticosteroids (class II). The pediatric patients showed improvement after 3 months of treatment.

The largest cohort of patients treated with topical retinoids was reported by Scardina et al. [23] who compared the clinical and histopathological efficacy of isotretinoin at two different concentrations (0.18 and 0.05%) in 70 OLP patients. They noted that none of the cases of reticular OLP showed clinical or histological improvement. In contrast, the atrophic-erosive forms showed significant improvement, both clinically and histologically. The disappearance of dysplastic phenomena was observed only at the 0.18% concentration.

Mastrangelo et al. [24] performed a scanning electron microscope analysis, before and after topical treatment with 0.1% isotretinoin, evaluating the morphostructural variation of the surface of the oral mucosa affected by OLP compared to healthy oral mucosa. They described that the epi-

thelial cells were more cohesive and the areas of desquamation were reduced; the cellular margins were more clear and regular in respect to the non-treated samples. The crests appeared more regular, ordered and combed, similar to that of the healthy mucosa. It was also possible to observe the presence of numerous microvilli in the non-desquamated cells on the surface of the crests.

Piattelli et al. [25], in their double-blind study, analyzed clinically, histologically and immunohistochemically the efficacy of topical treatment with isotretinoin 0.1% in 20 patients. Clinically they reported 10 complete and 10 partial responses to the treatment and after 3 years of follow-up, only 6 patients showed a relapse of the OLP lesions. Histologically, the specimens of patients who had been treated showed presence of hyperkeratosis and absence of parakeratosis. Immunohistochemically, Ki-67 and bcl-2 levels significantly rose following treatment, whereas apoptotic bodies decreased.

Based on the existing published literature, it is possible to confirm the therapeutic validity of topical retinoids on OLP. Their effects are documented clinically, histologically and ultrastructurally. They may represent an effective therapeutic alternative to corticosteroids or can be used in association to them. In fact, the consensus of the World Workshop in Oral Medicine IV recommended that topical retinoids should be considered as the second line of therapy for treating OLP [30].

Only few studies have compared the efficacy of retinoids on keratotic OLP and erosive OLP [11, 23, 25]. Sloberg et al. [11] reported improvement in 74% of keratotic lesions and a similar percentage (71%) in erosive OLP lesions. Scardina et al. [23] reported in erosive OLP patients 74.3% improvement when 0.18% isotretinoin was used and 25.7% improvement when the isotretinoin was less concentrated (0.05%). Surprisingly, the authors reported no improvement in reticular OLP. Piattelli et al. [25] demonstrated the same efficacy of isotretinoin 0.1% in reticular, plaque and erosive OLP. In the remaining studies, the authors did not discriminate their clinical results on the basis of the OLP clinical form. Whether keratotic OLP responds better than erosive OLP to topical retinoids is a question that deserves further comparative and controlled clinical trials. OLP with only white striae does not require any treatment because it is not painful and there is no risk of malignant transformation. On the other hand this is not the case for the white plaque form of OLP, maybe the best indication for treatment by topical retinoids.

Retinoids-related side effects are transitory and mild though particular precaution should be taken in regard to pregnant patients or those intending a pregnancy. Although the risk of embryopathies associated to topical retinoids is considered low, their use during pregnancy is not recommended because their risk/benefit ratio remains questionable [31]. One of the limitations of topical retinoids that emerged in some of the analyzed studies is the recurrence of OLP lesions after cessation of topical treatment with tretinoin and retinoic acid [10, 11, 13].

Evidence from existing studies shows that none of the OLP patients treated with retinoids developed oral squamous cell carcinoma. Even though the World Health Organization (WHO) has designated OLP as potentially premalignant, this topic is still very much debated. Therefore it is necessary to transmit warnings about potentially malignant disorders to patients, in line with recommendations by the WHO [32]. Retinoids are employed as antineoplastic agents and widely used in leukoplakia treatment [33]. From this point of view, their use in OLP, also in association with other drugs, may avoid the potential risk of neoplastic derailment although no controlled studies have demonstrated a protective and preventive effect of retinoids in the course of OLP. Further large, well-designed prospective randomized clinical trials should be carried out to evaluate with robust levels of evidence the benefits and harms of topical retinoids treatment in patients with OLP.

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