Int. J. Oral Maxillofac. Surg. 2006; 35: 67–71
doi:10.1016/j.ijom.2005.05.003, available online at http://www.sciencedirect.com

International Journal of
Oral & Maxillofacial Surgery

Clinical Paper
Oral Medicine

A randomized trial assessing the effectiveness of different concentrations of isotretinoin in the management of lichen planus

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G. A. Scardina, P. Messina, F. Carini, E. Maresi: A randomized trial assessing the effectiveness of different concentrations of isotretinoin in the management of lichen planus. Int. J. Oral Maxillofac. Surg. 2006; 35: 67–71.

Abstract. The aim of our 10-year study was to test the effectiveness of topical therapy based on 0.18% isotretinoin, comparing it with that most frequently used, i.e. at 0.05% concentration. Seventy patients with an established diagnosis of oral lichen planus were involved in the study. The patients were randomly divided into two groups, and the drug was administered topically at 0.05% and 0.18% concentrations.

The drug at the higher concentration, according to the same protocol, was administered to the patients who did not benefit from the therapy at the lower concentration. None of the cases of reticular lichen planus showed clinical or histological improvement. In contrast, the atrophic–erosive forms showed a significant improvement, both clinical and histological: in 26 patients (at 0.18% concentration) and in nine patients (at 0.05% concentration), the symptoms, as well as the erosions or ulcers observed, disappeared. The disappearance of dysplasic phenomena was observed at 0.18% concentration. Topical application of the drug was accompanied by an increase in soreness and pain, as well as greater sensitivity to hot foods. However, these side effects were transitory, and considered acceptable by the patients. The proposed therapeutic protocol was effective towards highly active atrophic–erosive oral lichen planus with dysplasic phenomena, which is the form of the disease at higher risk of malignant evolution.

Accepted for publication 3 May 2005

An accurate literature review has shown that Vitamin A and its derivatives have very important biological functions[2,3,5]. *In vitro* Vitamin A inhibits the malignant transformation caused by chemical carcinogenetic agents, ionizing radiations and viruses by interfering with the first phase of epithelial transformation, and such a preventive effect has proven useful even for oral mucosa cells[14,15].

In the pre-malignant state, the oral mucosa progresses through various grades of epithelial dysplasia, with the potential to convert to squamous cell carcinoma. Both topical and systemic retinoids were

0901-5027/010067 + 05 $30.00/0

found to suppress head and neck and lung carcinogenesis in animal models, and inhibit carcinogenesis in individuals with premalignant lesions and a high risk of developing cancer of the aerodigestive tract[7,8]. Following those studies, which have shown the important biological effects of Vitamin A and its derivatives, our study was aimed at evaluating the therapeutic effects of isotretinoin at different concentrations (0.05% and 0.18%) in the management of oral lichen planus (OLP)[9,24]. Often no medication is necessary for the benign form of this disease (reticular lichen planus). In the case of severe pain and a burning sensation, high-potency topical corticosteroids remain the most reliably effective treatment. Other available treatments are topical cyclosporine, tacrolimus, retinoids and other immunosuppressive agents. Systemic corticosteroids may be indicated in patients whose condition is unresponsive to topical corticosteroids. OLP remains a challenging disease to treat, in spite of the numerous treatments tried. Several studies have been carried out aimed at evaluating the effect of Vitamin A derivatives on OLP[1,4,6], but our study is characterized by histological monitoring before and after the treatment, by 10-year and 5-year follow-up of 19 and 20 cases, respectively, by evaluation of the timing of relapse, by application of different concentrations (0.05% and 0.18%) of isotretinoin, and by the method of administration of the therapy.

Materials and methods

Seventy patients (M/F: 30/40; mean age: 57.78 ± 8.9; range: 39–73), who from 1994 to 2004 came to our department for diagnostic investigations with a diagnosis of suspected OLP, were examined. Patients were always followed by the same operator. After accurate anamnesis and clinical examination, and having confirmed the diagnosis of suspected OLP, a histological sample was taken for final confirmation of the diagnosis. The biopsy was carried out under local anaesthesia with the punch technique in all the patients examined[13].

After histological confirmation of the diagnosis, the patients were included in the study if they gave their written consent after being properly informed about the therapeutic aspects of the experimental protocol. Patients with major disease (systemic manifestations) or those with histological diagnosis of carcinoma *in situ* were excluded from the study. Of the 70 patients involved, 37 were smokers and none were spirit drinkers. All the patients were informed about the importance of avoiding risk factors, such as smoking and alcohol, in order to reduce the possibility of lesion evolution and to make the treatment effective.

The patients were divided into two groups: to the 35 patients of group A was administered a galenic preparation based on 0.18% isotretinoin; to the 35 patients of group B isotretinoin was also administered, but at a lower concentration, i.e. 0.05%. The patients were randomly assigned to each group, since they were selected in order of access to our department. The drug was administered topically twice a day for three consecutive months; then it was suspended for 1 month, and the biopsy was repeated for histological follow up. The treatment used was not known to the patient or clinician. All the patients were advised to apply the drug to a gauze and then apply this to the lesion site. The use of gauze permits application for an adequate time period, reducing salivary interference. The patients were advised to keep the gauze in place for at least 10 consecutive minutes. The application was carried out twice a day, in the morning after breakfast and in the evening after dinner, and after accurate oral care. After three consecutive months of therapy, and after clinical and histological observations, the patients to whom the drug at lower concentration had been administered who did not show a clinical and histological improvement in the disease were treated with the drug at the higher concentration according to the same therapeutic protocol, and then evaluated again both at a clinical and a histological level.

Before starting therapy, all lesions were given a clinical score classifying the severity of OLP. The score ranged from 0 to 3 as follows: 3 = white striae with erosive area; 2 = white striae with atrophic area; 1 = white striae with no erythematous area; 0 = normal mucous. The visual analogue scale was used for the scoring of pain, with scores from 0 (no pain) to 10 (extreme pain). The Wilcoxon rank sum test was used for the analysis of the sign scores.

The galenical preparation was made in our laboratories, in a dark room, and stored in containers protected from the light by tinfoil. The drug was prepared at two different concentrations: 0.05% concentration, used in many published studies[12,20] and a higher concentration of 0.18%, chosen from our experience. The isotretinoin, taken from capsules marketed in Italy with the name of Roaccutan Roche, was included in 50 g of carboxymethylcellulose-based gel (marketed in Italy with the name of Oralbalance gel). After taking the isotretinoin from the capsules by means of 5 cc syringes, the active principle was included in the gel; subsequently, the preparation was homogenized. Then, the patients were advised to store the galenic preparation in the refrigerator.

During the first 3 months of treatment, the patients were observed every 15 days, to evaluate the clinical progress of the lesion and, above all, to check the method of application of the drug, which was prepared again before it was finished, as well as to evaluate any appearance of undesired effects. Subsequently, the treatment was interrupted for 1 month, and each patient was evaluated both from the clinical and the histological point of view, to monitor any lesion modifications. The patients continued to be followed to evaluate the preservation of the results obtained and any lesion relapse following therapy interruption. A group of 19 patients, in particular, had a 10-year follow up, while a group of 20 had a 5-year follow up. The drug (isotretinoin) was administered topically twice a day for three consecutive months; then it was suspended. These patients were examined every 12 months to evaluate the clinical and histological aspect of the lesions.

Results

The 70 patients with OLP showed different clinical and histological aspects. Ten cases had the characteristics of reticular lichen planus, 19 the aspect of white striae with an atrophic area, and 41 the aspect of white striae with an erosive area. Of the atrophic–erosive cases, nine showed dysplasia in progress or very high activity of the disease. In all the patients, the signs of the disease were located in correspondence with the right and left buccal mucosa, and also with the lingual back in 44 cases.

Prior to therapy, the average score of clinical severity was 2.4 and 2.5 in group A and group B, respectively. There was no statistically significant difference in clinical severity between the two groups ($P > 0.01$).

Symptoms were absent in patients with the reticular form (pain score = 0), whereas patients with the atrophic–erosive form reported soreness and pain, particularly while eating acidic and hot foods (average pain score = 8). In 13 cases, the patients reported difficulty in speaking (average pain score = 10). The patients with lingual localization also reported

Table 1. Results of treatment for patients in group a (0.18% concentration), group b (0.05% concentration), patients of group b treated with a higher dose (0.05 → 0.18% concentration), and at 10-year and 5-year follow-up

		Prior to treatment			After treatment		
Patients	Smokers	Histology	Appearance (mean scores)	Pain (mean scores)	Histology	Appearance (mean scores)	Pain (mean scores)
Group A = 35	17	Very high activity of the disease, 3 cases showed dysplasia	2.4	7.7	Epithelio-lesive activity decreased, dysplasia disappeared	1.3	0
Group B = 35	20	Very high activity of the disease, 6 cases showed dysplasia	2.5	7.8	Epithelio-lesive activity decreased, but dysplasia remained	2.1	4.2
0.05 → 0.18% = 22	8	Very high activity of the disease, 6 cases showed dysplasia	2.7	7.1	Epithelio-lesive activity decreased, dysplasia disappeared	1.1	0
Follow-up 10-year = 19	11	Very high activity of the disease, 4 cases showed dysplasia	2.1	7.2	Epithelio-lesive activity decreased, dysplasia disappeared	1.2	0
Follow-up 5-year = 20	14	Very high activity of the disease, 2 cases showed dysplasia	2.3	7.4	Epithelio-lesive activity decreased, dysplasia disappeared	1.2	0

taste alteration and considerable difficulty in eating.

Following application of the galenic preparation, modification of the clinical/histological pictures differed both according to drug concentration and the clinical characteristics of the disease. In all the cases observed, topical application of the drug caused, during the first 30 min, an increase in soreness and pain, as well as a greater sensitivity to hot foods. However, these side effects were transitory, and considered acceptable by the patients. No other undesired effects of the drug at either concentration were reported by the patients.

In the group of patients subjected to the drug at higher concentration, six had reticular lichen planus, while nine showed the atrophic form and twenty the erosive clinical aspect. After three consecutive months of treatment, the patients with reticular lichen planus did not show any modification in the clinical aspect of the lesion; in contrast, in 26 (74.3%) patients with the atrophic–erosive form, the symptoms, as well as the erosions or ulcers observed, disappeared. At a histological level, the picture was stationary in the reticular form; in contrast, in the atrophic–erosive form epithelio-lesive activity decreased and in three of these cases the dysplasia disappeared (Table 1).

In the second group of patients who received the drug at lower concentration, 4 had reticular lichen planus, while 10 showed the atrophic form and 21 the erosive clinical aspect. After three consecutive months of treatment, the patients with reticular lichen planus did not show any modification in the clinical aspect of the lesion; in contrast, in nine patients (25.7%) with the atrophic–erosive form, the symptoms, as well as the erosions or ulcers observed, disappeared. At a histological level, the picture was stationary in the reticular form; in contrast, in nine cases with the atrophic–erosive form epithelio-lesive activity decreased, but in six of these cases dysplasia remained; therefore, in 22 cases (62.8%) with a diagnosis of atrophic–erosive lichen planus, neither a clinical nor a histological improvement of the disease was observed (Table 1). The change noted in the patients receiving the drug at higher concentration was statistically significantly greater than that in the patients receiving the drug at lower concentration ($P < 0.01$).

The 22 cases with no clinical/histological modification were then administered the drug at the higher concentration: clinical and histological improvement was observed in 20 patients (91%) (Figs. 1 and 2; Table 1). Even the six patients with dysplasia at the post-therapy histological control showed improvement, with the disappearance of dysplasic phenomena.

Prior to therapy the average pain score was 7.7 and 7.8 in group A and group B patients, respectively ($P > 0.01$). At the end of therapy the average pain score was 0 and 4.2 in group A and group B, respectively ($P > 0.01$).

Of the 70 patients observed and followed during the 10 years of study, the original group was composed of 19 patients (6 with the reticular form, 5 with the atrophic form and 8 with the erosive form). The 10-year and 5-year follow-up patients are still under observation and show a completely asymptomatic picture; a relapse of the lesion occurred in only two cases, and was treated with the same therapeutic protocol (Table 1). None of the 70 cases involved in the study showed malignant evolution of the lesion.

Discussion

Several prospective and retrospective studies have reported OLP as having an

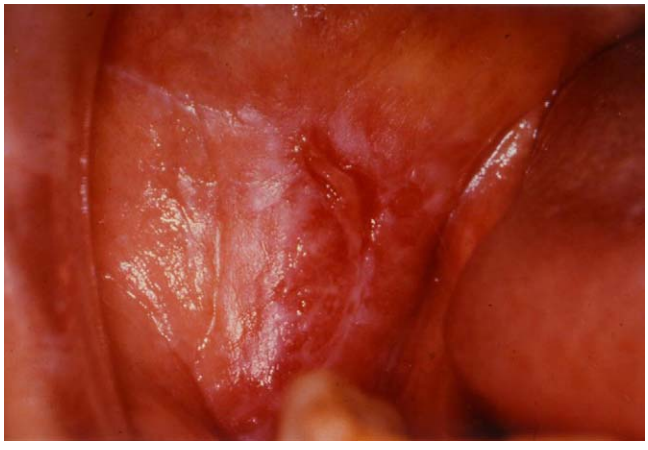

Fig. 1. Clinical aspect before therapy (isotretinoin 0.18%).

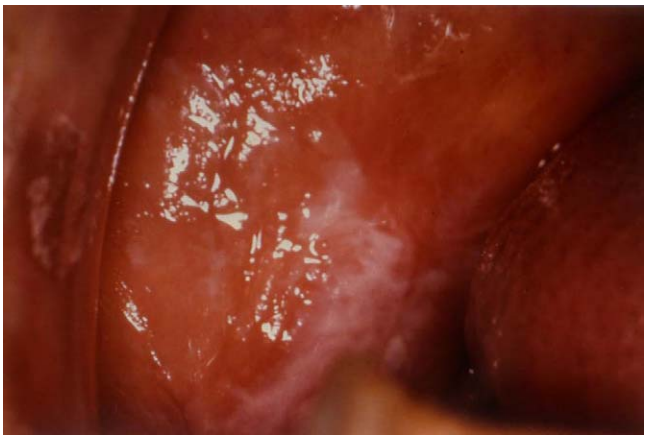

Fig. 2. Clinical aspect after therapy (isotretinoin 0.18%).

increased potential for malignant development; the reported transformation rates vary from 0% to 9%[10,18,19,23]. This is a matter of serious controversy: KRUTCHKOFF & EISENBERG stated that some of the reported OLP cases developing oral cancer were in fact not OLP, but rather dysplastic lesions with lichenoid features[16]. The implication of this observation is that patients with dysplasia represent a risk group, which can be identified by the appropriate use of available diagnostic methods and, as such, can be distinguished from patients with OLP with no dysplasia-related increased risk of development of oral cancer. The treatment of OLP remains a real challenge for clinicians who deal with this patient population and thus with diagnosis of this disease. The most effective treatment method to control the signs and symptoms of the disease is a short courses of systemic steroids and topical high-potency corticosteroids[11,25]. Other forms of therapy include the use of cyclosporine and retinoids, both systemic and topical[12,17,20,21,22].

Experimental studies of the therapeutic effectiveness of Vitamin A and its derivatives have shown continuous evolution. There have, over the years, been three main objectives: synthesis of new vitamin derivatives that result in lower accumulation in adipose tissue and lower organism permanence, and therefore also a reduction in undesired effects; finding the minimum effective dose; determining the most efficient method of administration[14,15].

Over the years, different opinions have been expressed regarding the effectiveness of OLP treatment by means of Vitamin A synthetic derivatives. Our study highlights two extremely important, innovative aspects of the treatment: the method of application of the drug and the concentration used. Regarding the first aspect, since the oral cavity is a wet environment, it is not easy to apply a drug and, above all, for it to remain on the lesions for a given time. The use of gauze reduces the cleansing effect of saliva, and also makes drug application fairly simple as reported by all the patients. As for the second aspect, none of the published studies used the same drug concentration as the present study (0.18% isotretinoin). We believe that our concentration is the most effective and acceptable to patients; a higher concentration could have undesired effects, such as soreness, which would make completion of the therapy cycle by the patients extremely difficult. We only observed a transitory soreness, which disappeared in the first 30 min after application. In our opinion, therefore, the frequently contrasting results on the effectiveness of Vitamin A synthetic derivatives in OLP therapy are mainly related to these two aspects.

The effectiveness of the therapeutic protocol varies according to the clinical and histological aspect of the lesion, the treatment being less effective when applied to the reticular form of the disease. The probability of malignant evolution of OLP is closely linked to its clinical and histological aspect. Since the reticular form is less prone to evolve into oral carcinoma, this variation in effectiveness does not limit the applicability of Vitamin A derivatives in OLP treatment. On the contrary, the study shows that our therapeutic protocol reduces the epitheliolesive activity of the disease. As regards dysplasia, the disappearance of this aspect was seen in all of the nine cases observed in the study. An important finding of our study is thus that the therapeutic protocol proves more effective against the forms of OLP at higher risk of malignant evolution at a histological level. From the clinical point of view also, a considerable effectiveness was observed in the resolution of erosive–ulcerous forms.

Of the 70 patients involved, 37 were smokers, and none were spirit drinkers. Another aspect worth mentioning is that of disease relapse. Our long clinical experience allows us to maintain that relapse is connected not so much to the therapy as to the intrinsic characteristics of the disease itself. Over the years, several patients showed a worsening of symptoms, accompanied by a worsening of the disease at both a clinical and a histological level. These 'relapses', however, were always controlled using the same therapeutic approach.

The administration method of our therapeutic approach is topical. This is important because the undesired effects of the therapy are reduced and made exclusively local and are, in any case, limited in time. Topical administration virtually eliminates the risk of teratogenesis, common to every therapy with Vitamin A derivatives. Also, it is known that systemic administration should be avoided in fertile women, and must be followed by contraceptive therapy for at least 2 years, since retinoids are deposited at the level of adipose tissue and slowly released. Topical administration makes our therapeutic protocol applicable in all those cases in which systemic corticosteroid treatment is contraindicated. Of our patients, five were hypertensive and nine diabetic; for these, corticosteroid therapy was not recommended. Topical corticosteroid application is often associated with fungus superinfection, which can make OLP management more difficult. The administration of clorexidine can control this problem, which was completely absent, however, with our approach. Given its effectiveness, our therapeutic approach can be considered valid not only for the cases in which classic systemic corticosteroid treatment is contraindicated, but for all cases of atrophic–erosive OLP.

In conclusion, the present study has demonstrated that isotretinoin, whether at 0.05% or 0.18% concentration, is an effective method of controlling the symptoms and signs of OLP when applied topically. Although the sample size is small, it would also appear that topical isotretinoin may reverse any dysplastic change associated with the disease. There is now a need to undertake a much more detailed randomized control trial to confirm these observations.

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