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Oral Leukoplakia – Topical Isotretinoin Treatment

Leukoplakia jamy ustnej – miejscowe leczenie izotretinoiną

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Abstract

Objectives. The goal of the research was to evaluate the effectiveness of topical isotretinoin in the therapy of oral leukoplakia.
Material and Methods. 40 patients with established diagnosis of oral leukoplakia were involved in the study. The drug was applied twice a day for two consecutive months. The patients were controlled every 15 days to evaluate the clinical progress of the lesions.
Results. The results showed a significant reduction in lesions (85%), with no documented topical or systemic adverse reactions.
Conclusions. The proposed therapeutic protocol was effective towards oral leukoplakia (**Dent. Med. Probl. 2005, 42, 1, 37–40**).

Key words: oral leukoplakia, isotretinoin, therapy.

Streszczenie

Cel pracy. Ocena skuteczności miejscowego zastosowania izotretinoiny w leczeniu leukoplakii jamy ustnej.
Materiał i metody. Do badań zakwalifikowano 40 pacjentów z rozpoznaniem leukoplakii jamy ustnej. Lek był podawany miejscowo 2 razy dziennie przez 2 miesiące. Pacjenci byli kontrolowani co 15 dni w celu klinicznego określenia progresji zmian.
Wyniki. Wykazano istotne ustąpienie zmian (85%) przy braku udokumentowanych miejscowych lub układowych reakcji niepożądanych.
Wnioski. Proponowany sposób leczenia był skuteczny w odniesieniu do leukoplakii jamy ustnej (**Dent. Med. Probl. 2005, 42, 1, 37–40**).

Słowa kluczowe: leukoplakia jamy ustnej, izotretinoina, leczenie.

An accurate literature review has shown that Vitamin A and its derivatives have very important biological functions. It regulates epithelial differentiation, it influences the immune system and some phlogosis mechanisms, it has a direct action on intercellular cohesion and interaction. Vitamin A deficiency can reveal itself with the formation of keratinized epithelium layers in correspondence with the oral mucosa while, on the contrary, its differentiation can be inhibited by an excess [1, 2]. *In vitro*, Vitamin A inhibits the malignant transformation caused by chemical carcinogenetic agents, ionizing radiations, viruses, interfering with the first phase of epithelial transformation, and such preventive effect has proven useful even for oral mucosa cells [1].

It has been observed that the promoting factors of tumoral forms increase the activity of one enzyme: ornithine decarboxylase. The latter limits polyamine synthesis involved in cell proliferation and differentiation. The retinol metabolic agents, instead, reduce ornithine decarboxylase activity. The induction of the latter probably occurrs during the G1 phase of the cellular cycle, and therefore

the retinol effects are most likely represented by the ability to block the cellular cycle in the G1 phase, due to ornithine decarboxylase inhibition. As a support to this thesis, there is the observation that the treatment of melanomatous cellular lines with retinoic acid increases the ratio in the G1 phase of their own cycle. Retinol shows a greater therapeutic effect before tumoral development [3–6].

Vitamin A also influences tumoral and cellular immunity: low doses of retinoic acid stimulate a cell-mediated response, whereas high doses inhibit it. The retinoic acid and its derivatives induce the activation of macrophages, making them highly cytostatic, with the consequent release of arginase, considered an important barrier against tumoral cells. It is possible that the role played by retinol on the macrophages is the result of prostaglandin inhibition since they inhibit the tumoricidal macrophages activity [7–9]. Glycosaminoglycan synthesis is also influenced by retinoids. Since these glycoconjugated agents are involved in cellular recognition and bonding, this may be a way through which retinoids influence differentiation but also the correct balance of oral epithelium [10].

Following the studies which have shown the important biological effects of Vitamin A and its derivatives, presented study was aimed at evaluating the therapeutic effects of isotretinoin in the management of oral leukoplakia (OL).

Material and Methods

40 patients (M/F: 18/12; mean: 56.69 ± 5.4; range: 48–65), who, from 1994 to 2004, came to authors' Department for diagnostic investigations with a diagnosis of suspected OL, were examined. Patients were always followed by the same operator. After accurate anamnesis and clinical examination, and having confirmed the diagnosis of suspected OL, a histological sample was taken for the final confirmation of the diagnosis. After the confirmation of the instrumental diagnosis of the pathology, 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. Out of the 40 patients involved, 35 were smokers, and 10 of them 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 drug was administered topically twice a day for two consecutive months. All the patients were advised to apply the drug to a gauze and apply this to the lesion site. The use of gauze permits the application for an adequate time, reducing salivary interference. The patients were advised to keep the gauze in place for at least 15 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. The Galenical preparation was made in authors' laboratories, in dark room, and stored in containers protected from the light by tinfoil. The drug was prepared at 0.18% concentration, chosen by authors' experience. The isotretinoin, taken from capsules marketed in Italy with the name of Roaccutan Roche®, was included in 50 grams 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 treatment, the patients were controlled every 15 days to evaluate the clinical progress of the lesion and, above all, to check the methods of application of the drug, which was prepared again before it was finished, as well as to evaluate any appearance of undesired effects. The intensity of whiteness of the OL was recorded photographically at baseline.

The patients continued to be followed in time to evaluate the preservation of the results obtained and any lesion relapse following therapy interruption. A group of 25 patients, in particular, shows a 10-year follow-up.

Results

The 40 cases of OL showed different clinical aspects. 10 cases had the characteristics of diffuse leukoplakia. The OL was located in correspondence with the buccal mucosa in 18 cases, with the lingual back in 15 cases, and with gingival mucous in 7 cases. The symptomatology was absent in all the patients. The patients with lingual localisation reported taste alteration. In all the cases observed, the topical application of the drug determined, during the first 30 minutes, erythema and xerostomia. However, the symptomatology was transitory, and considered acceptable by the patients. No other undesired effects of the drug were reported by the patients. After two consecutive months of treatment, 85% of patients showed complete clinical resolution of lesions (Fig. 1, 2).

Of the 40 patients observed and followed during the 10 years of study, the first original group

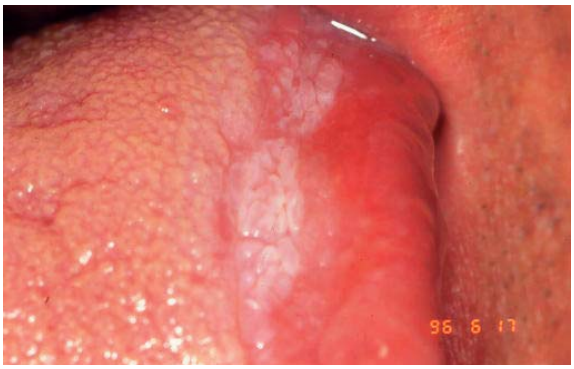

Fig. 1. Leukoplakia of the linqual back before therapy
Ryc. 1. Leukoplakia bocznej części języka przed leczeniem

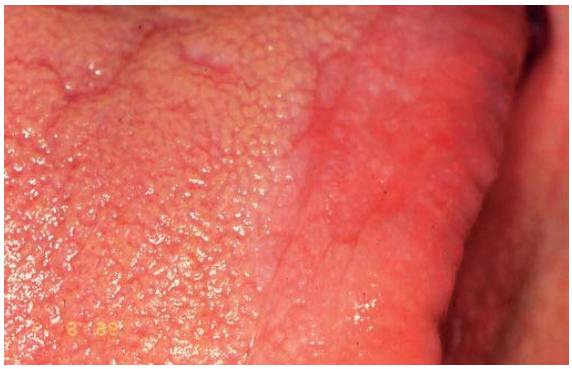

Fig. 2. Clinical state after therapy (isotretinoin 0.18%)
Ryc. 2. Stan kliniczny po leczeniu (izotretinoina 0,18%)

was composed of 25 patients. They are still under observation and show a completely asymptomatic picture; a relapse of the lesion occurred in only 2 cases, and was controlled again with the same therapeutic protocol. None of the 40 cases involved in the study showed a malignant evolution of the lesion.

Discussion

The study suggests that topical isotretinoin is effective in the therapy of OL. Topical anticancer drugs or retinoids are generally well tolerated, but their best indication is when the location or extent of the lesion render surgical removal difficult [7–9].

The treatment of OL remains a real challenge for clinicians who deal with this patient population and thus with diagnosis of this disease. Before a patient is started on therapy, a biopsy must be done and the diagnosis established.

The experimental studies of the therapeutic effectiveness of Vitamin A and its derivatives have shown a continuous evolution. In fact, over the years, an attempt has been made to reduce the limits of their use, and thus their side effects, mainly aiming at three objectives: synthesis of new vitamin derivatives which induce lower accumulation on adipose tissue and lower organism permanence, and therefore also reduction of undesired effects; minimum administered dose; method of administration [1, 4, 8]. Vitamins, such as A, beta carotene, C, E, B12 and folate, are the micronutrients with the strongest evidence of having a link to cancer prevention and control. Deficiency of these vitamins at the dietary, systemic or mucosal level will interact with tobacco use and increase the risk of oral precancerous lesions [5].

Over the years, different opinions have been expressed regarding the effectiveness of OL treatment by means of Vitamin A synthetic derivatives. According to the authors, two extremely important, innovative aspects introduced in the study are represented both by the method of application of the drug and the concentration of the preparation. Regarding the first aspect, in fact, since the oral cavity is a wet environment, it is not easy to apply a drug and, above all, to allow it to remain on the lesions for a given time. The use of gauze is a method to simplify the application, reducing the cleansing effect of saliva. It also makes drug application fairly simple, as reported by all the patients.

Another definitely important aspect is drug concentration; none of the studies present in literature, in fact, made use of a concentration as the authors did [4–6]. In consideration of the studies present in literature, the authors believe that the concentration is the most effective and acceptable to the patients as regards undesired effects; a higher concentration could have undesired effects, such as soreness, which would make completion of the therapy cycle by the patients extremely difficult. The authors only observed a transitory soreness, which disappeared, however, in the first thirty minutes after application. In authors' opinion, therefore, the frequently contrasting results on the effectiveness of Vitamin A synthetic derivatives in OL therapy are mainly related to these two aspects.

Over the years, a relapse of the lesion occurred in only 2 cases. These "relapses", however, were always controlled with the same therapeutic approach.

The element which shows treatment effectiveness is that a malignant evolution of pre-cancer occurred in none of the cases. Another aspect, which characterizes presented therapeutic approach, is the administration method, which is topical. This is important because the undesired effects of the therapy are reduced and made exclusively local and, in any case, limited in time. Moreover, the topical administration virtually

eliminates the risk of teratogenesis, common in every therapy with Vitamin A derivatives. In fact, it is known that the systemic administration must be avoided in fertile women, and however, it must be followed by contraceptive therapy for at least two years to avoid this risk, since retinoids are deposited at the level of adipose tissue and slowly released.

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