

Original Article

Oral lichen planus treated with tacrolimus 0.1%

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Abstract: Oral lichen planus (OLP) is considered a chronic autoimmune inflammatory disease and its presence may be related to increased emotional stress. The clinical relevance of OLP is the possibility of developing a squamous cell carcinoma, the etiology of which is still unknown. The aim of this study is to treat OLP lesions resistant to conventional treatment with corticosteroids, using topical tacrolimus 0.1% (Protopic[®]) twice a day for a period of eight weeks. Fifteen patients were selected who had filled out a history form and a visual analog scale for pain before and after treatment. All patients underwent an initial biopsy to diagnose the disease and another at the end of the treatment period to evaluate the effect of the medication on the infiltrate. A weekly check was carried out, observing the clinical appearance, pain symptoms and occurrence of side effects which, where present, were mild and transient. The results showed twelve patients (80%) with total or nearly total remission of pain symptoms and lesions, two patients (13.33%) showed clearer lesions and only one patient (6.67%) had no change in clinical symptoms or pain. Histopathological analysis showed OLP had a moderate or strong regression in twelve patients (80%) and an absent or mild regression in three patients (20%). Based on these results, it was concluded that tacrolimus 0.1% (Protopic[®]) is a safe and effective medication that improves the clinical appearance of the lesion, reduces pain as well as the histopathological features of OLP.

Keywords: Oral lichen planus, tacrolimus, treatment, recalcitrant, corticosteroids

Introduction

The prevalence of oral lichen planus (OLP) is relatively low (0.5% to 2.5%), being mainly associated with adult females at a ratio of 2:1, usually emerging in the 4th to 5th decade of life, where 10% to 15% of the patients with OLP also present cutaneous lesions [1-5].

The clinical presentation of OLP is interlaced white lines on an erythroplastic base known as "Wickham striae", these being symmetrical in most patients [3, 4, 6]. It is thought that this reaction is mediated by T lymphocytes, where the cells of the basal epithelial layer are recognized as foreign due to the change in the antigenicity of the surface of the cells [2, 3, 7-9], which is why it is considered to be a disease of unknown etiology and pathogeny occurring mainly in subjects with high stress levels [9, 10]. Currently OLP lesions are treated with different pharmacological options, and corticoids in their topical or systemic form are used frequently.

Topical tacrolimus is a powerful macrolide immunosuppressant to prevent transplant rejections of organs such as the kidney, liver and heart [1, 3, 5, 9, 11]. It is a topical non-corticosteroidal immunomodulator with a low adverse effect that presents a rapid response in the control of symptoms compared to traditional corticosteroids [11-13].

The anti-inflammatory molecular mechanism of action of tacrolimus is similar to cyclosporine, which inhibits the production of IL-2 by T lymphocytes [5, 14, 15] by inhibiting calcineurin phosphatase [6, 16], which in turn leads to the inhibition of the nuclear gene transcription of IL-2 cytosines and several other pro-inflammatory cytosines such as IL4 and IL5 [17]. As a result, activation and differentiation of inflammatory cells such as T lymphocytes, eosinophils or neutrophils are suppressed, which may explain why tacrolimus was also effective in subjects with cicatricial pemphigoid.

Table 1. Level of regression of the histopathological aspects between the first and second biopsy

Regression of structural histological aspects (RHS)	Level
Without regression	0
Mild regression	1
Moderate regression	2
Strong regression	3

The aim of this investigation is to analyze the behavior of tacrolimus 0.1% in subjects with OLP who have undergone previous conventional treatments without favorable results.

Materials and methods

This research protocol was approved by the ethics committee of the Universidade Federal de Juiz de Fora, Faculty of Dentistry. All the participants signed the informed consent and were informed of the scope of the study.

15 patients (11 female and 4 male) aged between 17 and 78 (age average 55 years) with symptoms associated with the disease were selected from the Department of Oral and Maxillofacial Surgery of the University Hospital of the UFJF and the Neoplasia Diagnosis Support Service of the UFJF. After the histopathological diagnosis of OLP, all the patients were treated with 20mg prednisolone for thirty days, and with unfavorable results were incorporated into the study.

Treatment protocol

One week prior to the start of the study, all treatments were suspended for all the patients. An incisional biopsy had been performed previously to confirm the histopathological diagnosis of OLP. Each patient began the proposed treatment with tacrolimus 0.1% (Protopic®) for two months (8 weeks) using it in topical form as a cream twice a day (every 12 h). The subjects were instructed to dry the place of application and apply a fine layer using compressed cotton and not to eat for 1 h after the application.

During the treatment period, the patients were evaluated weekly, recording the clinical appearance of the lesion, the symptoms of the disease and the occurrence of side effects. The treatment could be interrupted at any time that unwanted effects were determined by the research group or when the patients indicated termination of the study.

The visual analog scale (VAS) was used in all the evaluations; this was completed by the patient, determining the degree of severity of the pain and the symptomatology. In the eighth week a second biopsy was performed, following the same protocol for collection, processing and diagnosis as the initial biopsy in order to assess the action of the drug in relation to the histopathological aspects characteristic of OLP and also to confirm whether the pain symptoms and clinical appearance were related to the histopathological conditions. The scar from the first biopsy was used as a reference to perform the new biopsy laterally to it.

A quantitative histopathological evaluation was made by two different observers to evaluate the degree of regression or the condition of the tissue. That analysis was made using a scale from 0 to 3, classifying each of the selected segments (**Table 1**). Then the data were subjected to a descriptive statistical evaluation through McNemar's test and a paired t-test or a Wilcoxon test in case the variables did not respond to conditions of normality considering a value of $p < 0.05$ to achieve statistical relationship.

Results

All the patients presented symptoms of the disease for at least 1 year of evolution prior to the first therapeutic intervention. The most important symptoms observed were a burning sensation at the lesion site in 10 patients (3 patients with burning and pain, 2 patients with itching, and only one patient with burning, itching and pain at the same time). Three patients had only pain and 2 only itching in the area.

The visual analog scale before the treatment with tacrolimus 0.1% (Protopic®) presented variations from 4 to 9 (average 6.3) in the initial phase. The most detailed analysis of the results showed that the severity of the symptoms in 7 patients was severe pain with levels of 8 (**Table 2**).

After the first week of treatment unwanted effects were described in 6 patients (40%), of which 2 patients had dry mouth, one patient dry mouth and palatal changes and one patient reported burning at the application site; one patient presented dry mouth and a burning

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Table 2. Responses of the visual analog scale (VAS) in the initial stage (before beginning the treatment) and end stage (two months from beginning the treatment) of the 15 patients treated with tacrolimus 0.1%

Patients	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	X	SD	P
EVD a	9	5	9	8	8	6	5	7	5	4	4	5	8	7	5	6.3	1.73	0.001
EVD d	0	1	0	0	1	1	1	1	4	2	0	4	0	2	0	1.1	1.35	



Figure 1. Lesion of erosive OLP in the mucosa; an ulcerated leukoerythroblastic lesion with Wickham striae in its periphery is observed.



Figure 2. The same subject after 8 weeks of treatment demonstrating an oral mucosa free of lesions and regression of the pathology.

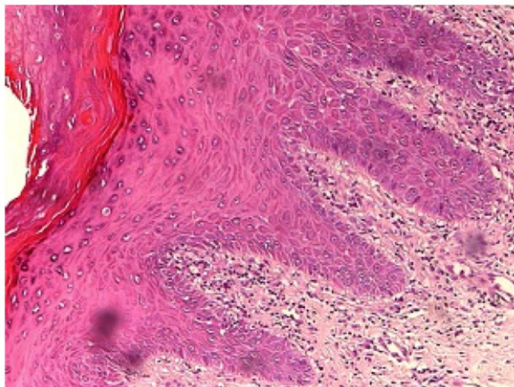


Figure 3. Histopathological analysis of the lesion where in the stage prior to treatment; epithelium is observed in serrated teeth, hyperkeratosis, hydropic degeneration of the base layer, acanthosis and predominantly lymphocytic inflammatory infiltrate in bundles of connective tissue (40X).

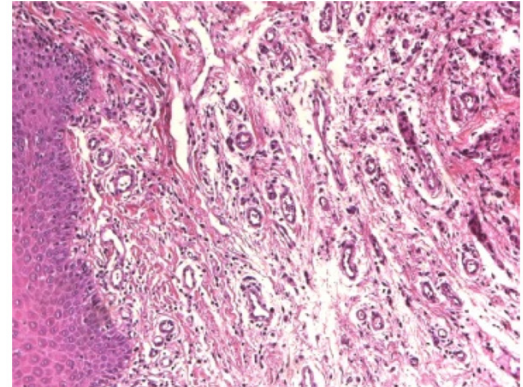


Figure 4. In the second biopsy (8 weeks later), a clean oral mucosa was observed with regeneration of the structural characteristics of the epithelium with the almost total absence of inflammatory infiltrate (40X).

sensation and one patient reported only changes in the palatal area.

It was not necessary to interrupt the treatment for any of the subjects because the side effects were temporary and mild, disappearing completely during the study period; nine patients reported no complications. In the first consultation of the clinical study, after one week, six

patients (40%) initially reported a decrease in OLP-associated symptoms, in five patients a slight improvement was noted (33.3%) and in four patients (26.64%) no change was noted. The clinical analysis showed no change.

The maximum improvement was achieved in the 4th and 5th week of treatment, where 12 subjects (79.92%) showed no type of pain or indicated that the discomfort was less and often imperceptible (79.92%) (Figures 1 and 2).

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In the clinical examination of the patients there were substantial improvements where the lesions disappeared completely or were almost imperceptible. Two patients were observed who, despite indicating an improvement, still presented clearer lesions; in one patient the symptoms did not change and no changes in the clinical appearance were observed either.

When the 8 weeks of the study were complete, a new VAS was conducted, presenting responses with a maximum variation between 0 and 4 with an average of 1.1 (Table 2), and when the initial comparison was set against the final one, it was observed that there was a significant difference ($p < 0.05$) between the two scales ($p = 0.001$). Twelve patients presented no pain symptoms or these were mild. In one patient who presented with moderate pain, this passed to mild and in two patients the symptoms remained constant throughout the treatment. Additionally, the statistical analysis of the data showed that the improvement in symptoms was related to the clinical improvements in the OLP ($p < 0.05$).

Comparison of the biopsies taken towards the end of the treatment with the initial biopsies revealed regression in the histopathological structures (RHS) of the OLP. This histopathological situation, as with the subject's VAS, presented statistically significant differences at the end of the treatment ($p < 0.05$) (Figures 3 and 4).

In terms of assessing the final clinical appearance of the lesions, the 12 patients (80.04%) with RHS of level 2 or 3 presented an almost total reduction or complete disappearance of the lesion and with non-existent or mild symptoms. In one patient (6.67%) with a RHS 1, the clearest lesion was observed and had a substantial improvement in the pain symptoms and of the two patients who had a RHS 0, one had the best defined lesion with the same symptoms as at the beginning of the treatment and the other had no changes in the clinical picture, pain or the histopathological structure.

After 5 months of evolution after the end of the treatment, of the 12 patients who had lesions that had practically or completely disappeared, two patients had a recurrence of the disease, with one of these presenting a new, smaller yet asymptomatic lesion with total surgical resection of the lesion, whereas the other patient

who had a recurrence of the disease with pain symptoms received new pharmacological treatment for the OLP.

Discussion

All the patients included in this study used daily doses of 20 mg prednisolone (once a day) for a period of at least 4 weeks before the initial biopsy without obtaining satisfactory results or remission of signs or symptoms. This indication was proposed by some authors [4, 18] where they reported that 20 mg prednisolone taken orally may be effective in the treatment of OLP without needing high doses to obtain a positive response.

There is a considerable number of patients who do not respond to conventional treatments, which is why there is a need to find new therapeutic modalities to control OLP that have fewer side effects [1, 13, 18, 19].

In this study, the topical application of tacrolimus 0.1% was indicated due to advantages such as the reduction of side effects and fast action in the control of symptoms [1, 12, 13]. The choice of the drug as a second line of treatment follows the direction taken by previously published works [10, 11, 16-18, 20] that show success in treatment with this drug.

The dosage used was the manufacturer's recommendation according to some studies [1, 5, 14] that showed this to be an efficient dosage; however, others suggest that application of the drug three times a day [21] or four times a day [15] may be more efficient. Additionally, the best results with tacrolimus 0.1% have been between the fourth and fifth week [1, 18, 19], which is also related positively to our results; others, however, show greater variation of this time for treatment [10, 11]. Our results presented the most subjective and objective (clinical) improvements between the 4th and 5th week. After 8 weeks there was an 80% improvement where the lesion was practically no longer perceptible. Even so, two patients presented deficiencies in their evolution, similar to that observed by other authors [21].

Using a quantitative analysis, the close relation between the improvement in clinical characteristics, improvement in symptoms and improvement in histopathological characteristics was observed [22], characterized by a reconstruction of the lining epithelium in the treated areas,

reducing epithelial hyperplasia and hyperkeratosis of the area.

Finally, in light of these results, the use of tacrolimus 0.1% is efficient in the control of lesions and the symptoms associated with the OLP that does not respond to other therapies with corticosteroids. Studies with a greater number of subjects must be conducted to be able to recommend the use of this drug at different stages of OLP.

Disclosure of conflict of interest

None.

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