Bull Group Int Rech Sci Stomatol et Odontol - Vol 38 n° 1-2, 1995

Cyclosporine A, an alternative to the oral lichen planus erosive treatment

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SUMMARY

We present a double blind study in two groups afflicted with Oral Lichen Planus erythematous of long evolution and resistant to other treatments. We tested on it a treatment with Cyclosporine A (CyA) which had been successfully used before by many dermatologists.

In the group A we used mouthwashes with a 5 ml Cyclosporine A solution to a 10% in olive oil of 0.4° of acidity for five minutes, three times a day for eight weeks. In the control group we used acetonide of triamcinolone 0,1% in aqueous solution. Patients in group A improved considerably in their symptomatology in a 90% against a 60% in group B. In group A we could appreciate a disappearance of the symptomatology after two weeks of treatment in 60% of patients against 30% in group B.

CyA can be an alternative to the conventional treatments in the acute period of lichen planus although it can not be considered as a first option drug because of the high cost of the treatment. For long term, results are not so good and we consider that extensive studies are necessary.

KEY WORDS:

Cyclosporine A, Lichen Planus Oral erosive, Treatment, Oral, Pathologie.

RÉSUMÉ

Nous présentons une étude en double aveugle qui a porté sur deux groupes de malades porteurs d'un lichen plan buccal de longue évolution et résistant aux traitements classiques. Nous avons essayé un traitement avec la Ciclosporine® qui avait réussi auparavant chez plusieurs dermatologues.

Le groupe A a essayé des rinçages avec 5 ml de solution Ciclosporine A à 10% dans de l'huile d'olive de 0,4° d'acidité, pendant 5 minutes, 3 fois par jour, pendant 8 semaines. Le groupe de contrôle a utilisé une solution de triamcinolone acetonide à 0,1%. A peu près 90% des malades du groupe étudié ont présenté une considérable amélioration de la symptomatologie, contre seulement 60% pour le groupe B. Après 2 semaines les symptômes ont disparu chez 60% des malades du groupe A, contre seulement 30% des malades du groupe B.

La Ciclosporine A peut être une alternative aux traitements conventionnels dans les périodes aigues du lichen plan. Cependant elle ne peut pas être considérée comme une drogue de premier choix étant donné son coût élevé. Pour évaluer les résultats à long terme il sera nécessaire d'entreprendre des études plus étendues.

MOTS-CLÉS:
Ciclosporine A, Lichen plan buccal érosif, Traitement, Bouche, Pathologie.

INTRODUCTION

Cyclosporine A (CyA), is an immune depressor drug, not myelotoxic (Borel, 1982), with specific activity on T-lymphocytes (Liter, 1986). It was isolated by Dr. Borel beginning with a metabolite of the Tolypocladium inflamatum fungus (Wenger, 1990); now it is possible to obtain it in a synthetic form.

From the beginning it showed an unquestionable utility on patients who had been subjected to organ transplants (Lorber *et al.*, 1990 and Kahan *et al.*, 1990 and Diaz LLopis *et al.*, 1990 and Alfonso *et al.*, 1990). New indications for these medications are now being established, especially on diseases of autoimmune etiology. There are many publications that document the use of this drug in patients with autoimmune diseases and who are resistant to the more classic therapeutics.

In ophtalmology it has been used in the treatment of Behçet's disease (Diaz LLopis *et al.*, 1990) and in other types of uveitis (Alfonso *et al.*, 1990). In hematology it has been used in the Sézary's syndrome (Ramon, 1988) and in the pure aplasia of red cells (Rioperez *et al.*, 1987). Its use has also been tested on Crohn's disease (Moreno *et al.*, 1988), ulcerous colitis (Lichtiger and Present, 1990), primary biliary cirrhosis (Wiesner *et al.*, 1990) and on other diseases of the digestive tract (Morales *et al.*, 1989 and Seidman *et al.*, 1990). Good results have been obtained on the myastenia gravis (Nyberg-Hansen and Gjerstad, 1988) and it has also been tested on multiple sclerosis (Rudge *et al.*, 1989) and on other neurologic diseases (Hodgkinson *et al.*, 1990). Studies of the use of the drug on the nephrotic syndrome (Simon *et al.*, 1990), the insulin-dependent diabetes (Atkinson *et al.*, 1990) and the rheumatoid arthritis (Corvetta *et al.*, 1990 and Alegre *et al.*, 1990) have been published.

In dermatology, it has been successfully used on diseases such as psoriasis (Boixeda *et al.*, 1991 and Ellis *et al.*, 1991), lichen planus (Ho *et al.*, 1990 and Pigato *et al.*, 1990 and Gupta *et al.*, 1989), pemphigus vulgaris (Bondesson and Hammar, 1990) and pemphigoid, mycosis fungoides and systemic lupus erythematous (Jensen *et al.*, 1987 and Isenberg *et al.*, 1981).

The CyA has been topically used on the alopecia areata (Thomson *et al.*, 1986) and, more recently, on the oral lichen planus (Frances *et al.*, 1988 and Eisen *et al.*, 1990 and Rosello *et al.*, 1992).

These studies led us to use the CyA in form of mouthwash on two patients who were afflicted with oral lichen planus (OLP), symptomatic and refractory to the traditional treatments.

METHOD

We present a double blind study in two groups of 10 patients every each afflicted with OLP from whom we had histological confirmation of the clinical diagnosis. We start the study in August of 1992 and finish in February of 1994. When we started the study, these patients fulfilled the following requirements:
a. they had three acute clinical episodies in the last year.
b. they did not present systemic concomitant diseases that could endager the treatment.

During the treatment, the patients were examined once a week to value the results and the appearance of possible complications.

The treatment in the group A consisted of mouthwashes with 5 ml of CyA solution (Sandimum®) with a 10% dilution in olive of 0.4 of acidity, for five minutes, three times a day for eight weeks. After each mouthwash the patient had to re-

main 30 minutes without ingesting food or liquid. In the group B we used a conventional treatment with aquous solution of acetonide of triamcinolone to a 0,1% four mouthwashes (Chimenos *et al.*, 1993).

To systemize the results, we analize symptoms, erosion, erythema and reticulation. Symptoms are analyzed by the patient from 1 to 10. Erythema and erosion are valued by the professional from 1 to 10 and reticulation is valued with a millimetred paper.

Fig. 2: This chart shows the % of improvement of erosion for each patient in the end of study (8 weeks).
Fig. 2: Amélioration de l'ulcération pour chaque patient à la fin de l'étude (8 semaines), exprimé en %.

RESULTS

So, we considered three parameters to be able to systemize the results: the symptoms, the erythema, and the erosion.

The *symptoms* decreased on a considerable way in group A, the patients referred a relief of pain and were able to ingest substances that before the treatment they had completely forbidden, such as acid fruits and spices, and also tolerated the ingesta of substances at extreme temperatures. Patients in group A manifested an improvement of 90% for 80% of them, and of these 6 referred it in a 100% against 60% and 30% for group B, Fig. 1.

The decrease of the *erythema* and the *erosion* of the buccal mucosa of the patients was important from the third week of treatment on, getting an improvement of an 78% and 81% of mean in group A and of a 62% and 62% in the group B, Fig. 2 and 3.

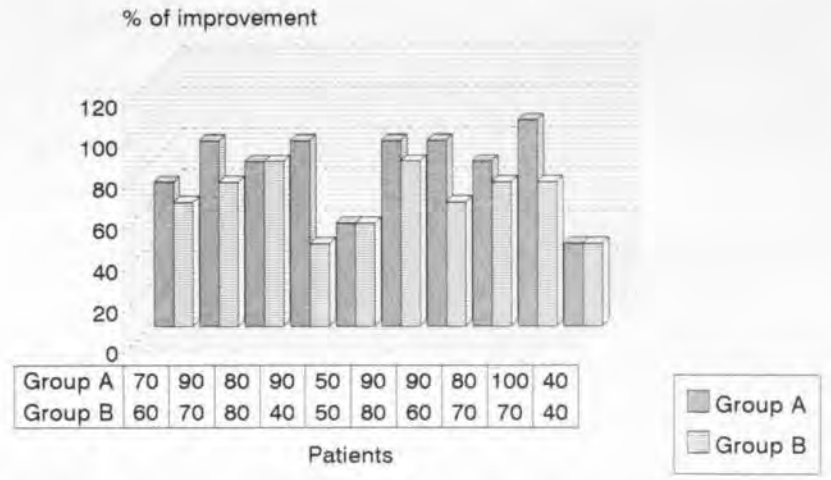


Fig. 3: This chart shows the % of improvement of erythema for each patient in the end of study (8 weeks).
Fig. 3: Amélioration de l'érythème pour chaque patient à la fin de l'étude (8 semaines), exprimé en %.

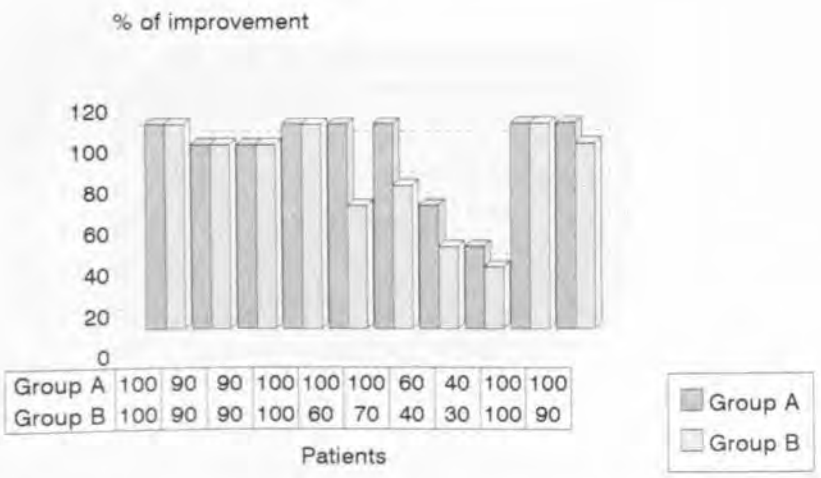


Fig. 1: This chart shows the % of improvement of symptoms for each patient in the end of study (8 weeks).
Fig. 1: Amélioration des symptômes pour chaque patient à la fin de l'étude, exprimé en % (8 semaines).

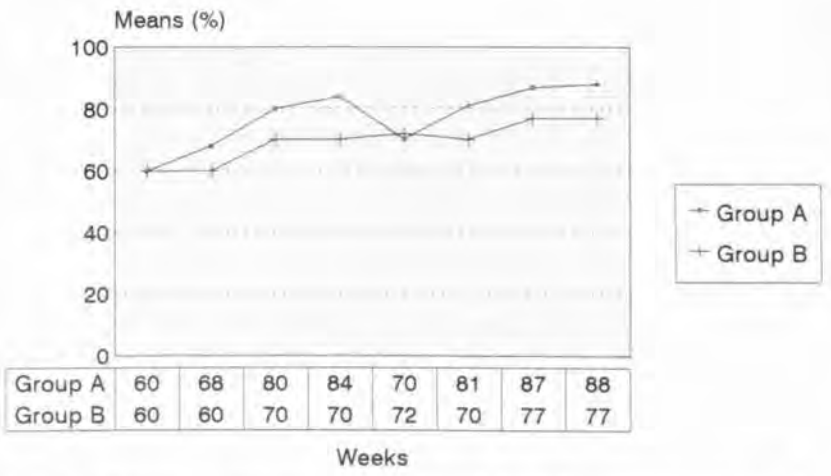
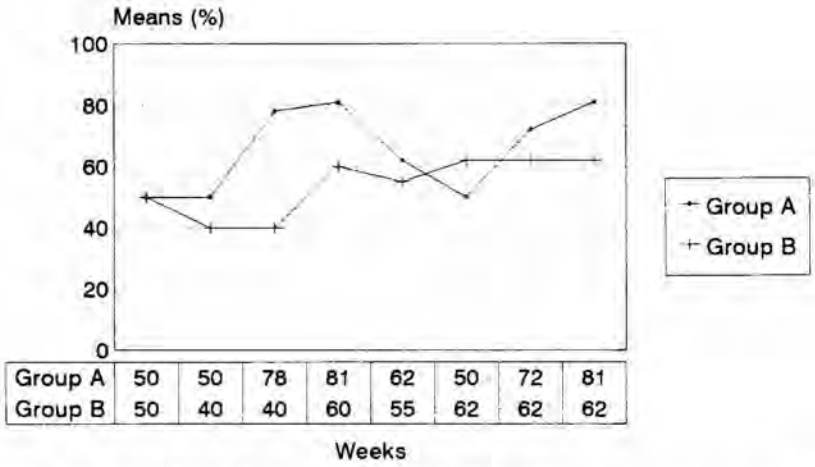


Fig. 4: This chart shows the means of weekly improvement of symptoms for each group.
Fig. 4: Amélioration des symptômes pour chaque groupe, exprimé en moyenne hebdomadaire.

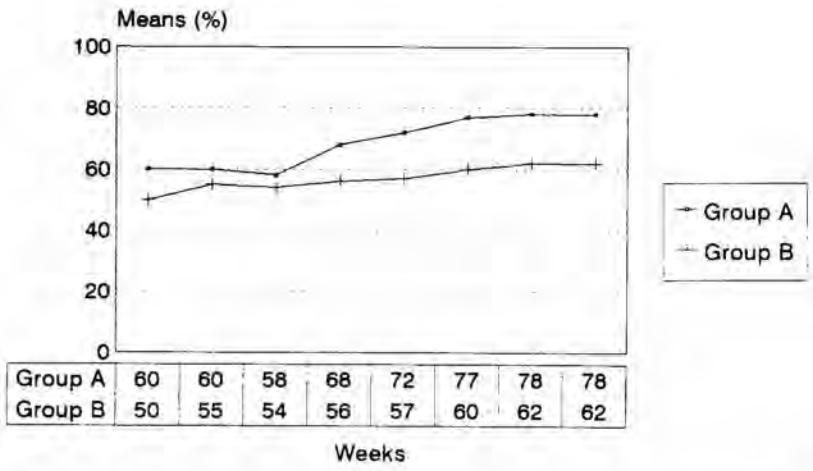
In the Figures 4, 5 and 6 we show the evolution on time of the evalued parameters for both groups.

In ten months after the study the percentage of recidives was 20% in group A and 30% in group B.



Group A	50	50	78	81	62	50	72	81
Group B	50	40	40	60	55	62	62	62

Fig. 5: This chart shows the means of weekly improvement of erosion for each group.
Fig. 5: Amélioration hebdomadaire moyenne de l'érosion pour chaque groupe.



Group A	60	60	58	68	72	77	78	78
Group B	50	55	54	56	57	60	62	62

Fig. 6: This chart shows the means of weekly improvement of erythema for each group.
Fig. 6: Amélioration hebdomadaire moyenne de l'erythème pour chaque groupe.

DISCUSSION

The OLPe is a mucocutaneous disease with a probable autoimmune aetiology (Balato *et al.*, 1989). When we study the afflicted tissues we observe an infiltrate on which the T-helper lymphocytes predominate at the early stages of the disease, detecting a relative increase of the T-killer lymphocytes when the lesions (Mozzanica *et al.*, 1991) then tend to be chronic. In this infiltrate we can also find increased the values of the other mediators of the immune response of the organism, such as interferon gamma or the ICAM-1 activity of the keratinocytes.

This increase of the immunological activity of the lesions gave us the theoretical justification to use the CyA in the treatment of the OLP.

The classic therapeutics of the OLP with retinoids and/or corticoids has not always proved satisfactory (Zegarelli, 1983, 1984 and Camisa and Allen, 1986), and we must bear in mind the possible complications of the prolonged use of these drugs, as well as their absolute contra-indications in certain patients (Freitag and Miller, 1982).

Other medicines such as the dapsones (Beck and Brandrup, 1986) or the psoralens associated to therapy with UVA radiation in the oral cavity (Helander *et al.*, 1987) have not obtained completely satisfactory results. Other substances, such as the griseofulvin are even more debated, and good results have been published (Aufdemorte *et al.*, 1983) while other authors advise against them completely (Bagan *et al.*, 1985).

The fact that there is not medication completely effective for the treatment of the OLP makes it necessary to keep looking for a substance capable of resolving the problems these group of patients suffer. We think that the results we have obtained with our group of patients vouch for the possibility of considering the CyA in topic application as an alternative to those cases of OLP resistent to the conventional treatments, as other authors point out too (Levell *et al.*, 1991 and Frances *et al.*, 1988 and Eisen *et al.*, 1990 and Rosello *et al.*, 1992).

The mechanism of action of the CyA on the OLP would be based on the inhibition of the action of the T-helper lymphocytes, as well as on the production of interleukin 2 which is a necessary mediator for the activation of the T-cytotoxic lymphocytes. It would also be responsible for the inhibition of other mediators such as the interleukin 1 and the interferon gamma (Chimenos *et al.*, 1993 and Lemaire *et al.*, 1990).

The long experience of the use of the CyA on transplanted patients (Awni *et al.*, 1990, Lorber *et al.*, 1990 and Kahan *et al.*, 1990) and the very low systematic absorption detected on the topic treatment of the LPO with doses 10 times higher than the

one we used (Eisen *et al.*, 1990 and Rosello *et al.*, 1992), makes us postulate a low risk for the use of this drug in long-term treatments.

An important problem is the high market cost of the product. If we use a 10% dilution, which was successfully used before by Dr. Alegre and colleagues in the Dermathology Service of the University Hospital in Valencia, the problem is somewhat obviated, but the economic cost of the treatment is still high.

CONCLUSIONS

In view of the obtained results in our patients and resting on the results that other authors have communicated, we consider that the CyA would constitute a valid alternative for the treatment of the OLP but, its results are very uncertain to control long term pathology.

The high economic cost of the treatment implies that we can not consider CyA as a drug of first choice in the treatment of the erosive LP, reserving it for these cases where the conventional therapeutics are not effective or are contraindicated.

Clearly, it is necessary to undertake more extensive studies and at longer term, so that we can value the ability of this new indication of the CyA.

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