Journal section: Oral Medicine and Pathology
Publication Types: Research

Effectiveness of substituting cyclosporin A with tacrolimus in reducing gingival overgrowth in renal transplant patients

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Received: 18/11/2008
Accepted: 20/03/2009

Párraga-Linares L, Almendros-Marqués N, Berini-Aytés L, Cosme Gay-Escoda. Effectiveness of substituting cyclosporin A with tacrolimus in reducing gingival overgrowth in renal transplant patients. Med Oral Patol Oral Cir Bucal. 2009 Sep 1;14 (9):e429-33.
http://www.medicinaoral.com/medoralfree01/v14i9/medoralv14i9p429. pdf

Article Number: 2565 http://www.medicinaoral.com/

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Indexed in:
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-JOURNAL CITATION REPORTS
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Abstract

Objectives: This study aims to evaluate the effectiveness of periodontal therapy combined with tacrolimus in the suppression of gingival overgrowth (GO) and the effect on GO of changing from cyclosporin A to tacrolimus.

Patients and Methods: Sixteen renal transplant patients, averaging 52 years of age, whose kidney function was stable and were receiving treatment with cyclosporin A, were randomly assigned to one of two groups. In the experimental group, patients were instructed in oral hygiene and underwent periodontal treatment, whereas in the control group, only oral hygiene instructions were given. After the first visit and the change of medication from cyclosporine to tacrolimus in both groups, periodic clinical revisions were carried out for 3 months in order to assess the evolution of GO.

Results: All patients showed a progressive decrease in GO. There were no statistically significant differences between the two groups ($p>0.05$). A greater decrease in GO occurred within the first month after changing the medication.

Conclusions: No improved effectiveness in reducing GO was observed for periodontal therapy in combination with tacrolimus. Tacrolimus is an alternative to cyclosporine when attempting to avoid GO in patients with kidney transplants.

Key words: *Gingival overgrowth, immunosuppressants, tacrolimus, cyclosporin A kidney transplant.*

Introduction

Cyclosporin A is a lipophilic cyclic oligopeptide extracted from a fungus (*Tolypocladium inflatum Gams*) with immunosuppressant action widely used to inhibit organ transplant rejection, and in the treatment of autoimmune diseases such as insulin-dependent diabetes mellitus, Behçet disease, psoriasis, lupus erythematosus or rheumatoid arthritis (1).

Adverse effects associated with immunosuppressive therapy with cyclosporin A have been reported, such as: Hypertension, usually associated with fluid retention; nephrotoxicity, by altering the balance between prostacyclin and thromboxane A2, liver toxicity, neurotoxicity and diabetes mellitus. In addition, patients treated with this drug have a higher incidence of skin tumors and lymphomas, particularly Kaposi's sarcoma.

Adverse oral effects are hypertrophy of lingual fungiform papillae and gingival overgrowth (GO) (2,3). Spolidorio et al. (4), compared the oral health of patients treated with cyclosporine or tacrolimus and found cases of squamous cell carcinoma, herpes simplex, GO and candidiasis (found to be the most common oral pathology) in the group of patients treated with cyclosporine. Clinically, GO may manifest as non-inflamed, firm, fibrous gingiva, or with an edematous, erythematous, hemorrhagic appearance in cases associated with gingivitis induced by bacterial plaque (5). The location of the plaque and gingivitis is not consistent with the distribution of the GO, suggesting a possible influence of local anatomical features (insertion of frenum, tongue) in the development of GO (6).

No consensus exists in the literature on the relationship between dosage and the concentration of cyclosporin A and the development of GO. Daley et al. (7) suggested that a concentration threshold of cyclosporine had to be exceeded for GO to appear, while higher concentrations of the drug did not increase the severity of the GO.

Histologically, GO is characterized by areas of dense collagen and degeneration associated with an inflammatory infiltrate of lymphocytes and plasma cells. Likewise, there is no evidence of an increase in the number of fibroblasts (8).

In contrast, the immunosuppressant, tacrolimus, has been used successfully in liver and kidney transplants with no adverse effects on the gingiva. However, it is associated with an increased incidence of post-transplant diabetes mellitus when used at high doses, in conjunction with corticosteroids and in patients older than 45 years (9).

A rapid resolution of GO has been observed after conversion from cyclosporin A to tacrolimus. Tacrolimus is a macrolide derived from a fungus (*Streptomyces tsukubaensis*), introduced in 1987 to prevent rejection of transplanted organs. It displays immunosuppressive characteristics similar to those of cyclosporine, but is between 10 and 100 times more effective in inhibiting IL-2 and interferon gamma (IFN-γ) production (10). The adverse effects of tacrolimus are similar to those of cyclosporine, and associated nephrotoxicity and hypertension are lesser severe. This may, therefore, be a good alternative to cyclosporin A when avoiding GO in renal transplant patients is desired.

This paper aims to evaluate the efficacy of tacrolimus therapy in reducing GO in renal transplant patients previously treated with cyclosporin A, as well as the effect of conventional periodontal treatment on the amount of decrease.

Patients and Method

We performed a prospective randomized clinical trial in which 16 patients were included (10 males and 6 females) aged between 31 and 67 years, having undergone kidney transplant at the Bellvitge Hospital in L'Hospitalet de Llobregat (Barcelona). Renal function of all patients was stable and they were under immunosuppressive therapy with cyclosporin A.

Patients who had undergone periodontal treatment within the previous 6 months, smokers, those treated with hydantoin, nifedipine, amlodipine, verapamil and diltiazem and / or with an associated systemic disease that could have a known affect on the gingiva such as thrombocytopenic purpura, leukemia or diabetes mellitus, were excluded from the study.

All patients included in the study were required to have at least 10 anterior teeth.

After being informed of the nature of the study and having obtained informed consent to participate in the research, patients were randomly assigned to two groups. On the first visit, the experimental group was instructed in oral hygiene, and periodontal treatment was conducted consisting of the removal of plaque and supragingival calculus; while in the control group, only verbal instructions for oral hygiene were given. After the first visit, cyclosporin A was substituted by tacrolimus in all patients. Follow-up was performed monthly for 3 months. All examinations were carried out by two dentists at the Oral Surgery Service of the Dental Clinic at the University of Barcelona.

At the first visit and on all subsequent checkups, GO was assessed in the incisor-canine region in both jaws using the Angelopoulus and Goaz, and M and B indexes.

The first assesses vertical or apical-coronal GO, using values ranging from 0, when GO is absent; to 3, if the enlargement is severe and covers more than two thirds of the tooth crown. Six points are assessed at each tooth: middle, distal and mesial at the facial and palatal or lingual aspect.

The second evaluates overgrowth in a horizontal or buccolingual direction of the interdental papilla both on the buccal and palatal or lingual side. Values range from

0 to 2, with a thickness of less than 1 mm interdental papilla for the value 0,1 for interdental papilla thickness between 1 and 2 mm, and 2 for interdental papilla thickness greater than 2 mm.

Statistical analyses were carried out using the following non-parametric tests: Mann-Whitney, Friedman and Wilcoxon. In all cases, values of $p<0.05$ were considered statistically significant.

Results

The average age of the patients included in the study was 52 years, 62% were men and 38% women. During the study, one of the 16 patients was lost suffering from hyperglycemic coma one month after the administration of tacrolimus and the suppression of cyclosporin A.

All patients showed a progressive decrease in GO. There were no statistically significant differences ($p>0.05$) between the experimental and the control group. However, neither group obtained a complete remission. (Fig.1 and 2) show a patient who presented almost complete remission of his GO after switching to tacrolimus as monotherapy.

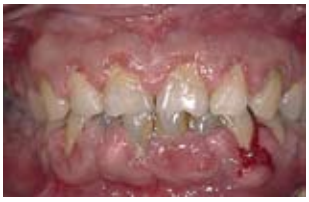

Fig. 1. Gingival overgrowth at the first visit.

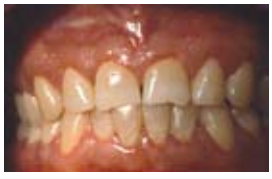

Fig. 2. The same patient 3 months after changing from cyclosporin A to tacrolimus.

Differences in the Angelopoulus and Goaz index were detected only at 3 buccal points two months after the change in medication. However, in the M and B index, 5 of the 6 points that showed differences between the experimental and the control group were palatal; most of these differences were also seen at the 2 month examination.

The largest decrease in GO occurred during the first month after the change in medication. Thereafter, the GO stabilized, but with continued trend for improvement. At the second and third month follow-up, there were no statistically significant changes, except for the interdental papilla distal to 3.3 in a buccolingual direction (M and B index) in the control group.

On reviewing the evolution of GO from the first visit to the last examination at 3 months after changing medication, using the Angelopoulus and Goaz index no statistically significant changes ($p>0.05$) were observed in any of the buccal, palatal or lingual midpoints (Table 1).

A greater decrease in GO was observed at the distal and mesial points in both maxilla and mandible.

Likewise, the reduction of GO in the experimental group and the control group was unequal between the mandible and the maxilla. In the mandible, the points evolved in a similar manner in both groups, whereas in the maxilla the experimental group presented more points with favorable results. These were located mostly in the second quadrant.

Discussion

Gingival overgrowth is a commonly associated complication with the use of drugs such as cyclosporin A, which can cause oral and psychological changes in the patient. Tacrolimus is a therapeutic alternative to cyclosporin A (11), having some similar, although decreased, adverse effects. In the study by James et al. (12), there was an

Table 1. Results of measurements using Angelopoulus and Goaz Index, and M and B Index (Mann-Whitney Test), made between the study group and the control group from the first to the last visit.

Angelopoulus and Goaz Index		**M and B Index**	
Mean cases	Mean controls	Mean cases	Mean controls
12MBv3* 0	0.75	11DPv2** 0.13	0.75
11DBv3 0	0.75	21MPv2 0.13	0.63
42DBv3 0	0.63	22MPv2 0	0.50
		21MPv3 0	0.50
		22MPv3 0	0.50
		32MPVv3 0.13	0.75

*v3: 3th visit
**v2: 2th visit
(M,D,V,P): mesial, distal, bucal y palatal

increase in gingival growth of 24.9% to 82.3% with the change from tacrolimus to cyclosporine.

GO affects the attached gingiva, it may extend coronally and interfere with occlusion, mastication and phonation. It usually begins in the interdental papilla during the first 3 months of treatment with cyclosporin A (13). However, some authors have only seen GO in patients treated with cyclosporin A for more than 3 months. In our study, GO evaluated using the Angelopoulus and Goaz index was less than 1, and therefore did not interfere with occlusion.

GO in patients treated with cyclosporin A is more severe in areas with plaque, calculus, subgingival restorations, as well as in wearers of orthodontic appliances and prostheses (7). However, the role of plaque in GO induced by cyclosporin A remains uncertain. Alfonso et al. (13), in a study of 40 patients, found no statistically significant relationship between GO and the plaque index. The elimination of bacterial plaque appears to have little relevance in the prevention of GO. In our study the presence of plaque was not associated with an increase in GO, but did have an effect on its evolution.

The incidence of GO in patients who continue treatment with cyclosporin A varies from 13% to 81%. The reasons for this wide margin are, the nature of the disease treated, the patient's age, the dose and duration of treatment with cyclosporin A, the combined use of other drugs and genetic predisposition. In a study by Vescovi et al. the prevalence of GO was 47% in patients taking cyclosporin A with azathioprine, and 50% for those who only took cyclosporin A. In our study the incidence of GO in patients taking cyclosporin A was 73%. The prevalence and severity of GO is increased in individuals who take cyclosporin A with calcium channel-blocking agents (4,6). James et al. (14) in their study concluded that coadministration of cyclosporin A with amlodipine produces a greater GO (72%) than cyclosporin A with nifedipine (53%). In our study, all patients taking additional medications were excluded to avoid bias in the results.

Daley et al. (15) demonstrated that children and adolescents were more susceptible to gingival changes induced by cyclosporin A. As our sample did not include children or adolescents, our results cannot be compared with these facts.

Although GO caused by the intake of cyclosporin A may be found in any region of the oral cavity, the changes are most pronounced in the anterior area of the mandible and on the buccal side. A study conducted on 194 patients undergoing an organ transplant confirmed the predilection of GO for the vestibular surface, but no statistically significant differences were found between maxilla and mandible. Said GO was higher in the canine region than in the area of the central incisors (6). In our study, however, the decrease of GO in the experimental group and the control group was not equal in the mandible and the maxilla. In the mandible, points evolved similarly in both groups, whereas in the maxilla the experimental group presented more points with favorable results. Furthermore, no statistically significant differences were observed in the vestibular points, the more pronounced changes being in the mesial and distal points. The most favorable evolution was found in the second quadrant in the experimental group.

The removal of the inducing drug, in this case cyclosporin A, would be the ideal choice, since it has been shown that the GO disappears completely 3-12 months after drug suspension. However, this measure is not always possible in patients with kidney transplants. In our study, the largest decrease in GO occurred in the first month after change in medication.

There have been cases reported in which there was a remission of GO after reducing the dosage of cyclosporin A, and without recurrence after a follow-up of 2 years. This finding raises the possibility that a reduction in the dosage of cyclosporin A below a threshold concentration may resolve the GO (16).

In a study by Oliveira et al. (17) to determine the prevalence and severity of GO in patients treated with tacrolimus or cyclosporin A; in patients treated with tacrolimus a 17.9% prevalence of GO was noted, while in the group medicated with cyclosporin A this was 38.1%. However, no statistically significant differences were observed between the clinical variables (plaque index and papillary bleeding index) in either group. In the study by Ellis et al. (18) on the prevalence of gingival growth in transplanted patients, the GO was rated as 14.15% in patients treated with tacrolimus and as 22.4% in patients treated with cyclosporin A, proving once again that tacrolimus produces less GO than cyclosporin A. They also identified independent variables that reduce GO, the most relevant being the age and combined administration of azathioprine. Other variables that increased GO were medication combined with calcium channel blockers, a high plaque index, papillary bleeding, and previous medication with cyclosporine (18).

The results obtained in this study are consistent with others previously published, making it possible to state that the use of tacrolimus is associated with a substantial reduction in the severity of GO, although the reduction is not complete in most cases (12). On the other hand, we found recent studies that conclude that there is no statistically significant difference in the incidence of GO in patients treated with tacrolimus compared with others treated with cyclosporine 90 days after transplantation (19). A study by Hernandez et al. (20) confirmed that this reduction was already evident 8 weeks after the conversion from cyclosporine to tacrolimus, coinciding with the results of our study.

The partial disappearance of GO may be explained by

the short follow-up period on the patients in our study. Three months is not sufficient to achieve a physiological remodeling, which involves the removal of a large number of macromolecules of the extracellular matrix. In spite of this, all patients expressed their satisfaction with the elimination of the functional and aesthetic irritation following change in medication.

Previous studies that have assessed the effects of periodontal treatment on GO showed conflicting results. Kantarci et al. (1) claimed that good plaque control through proper oral hygiene, and periodontal treatment which consists in removing supra- and sub-gingival plaque and calculus, should be the first step in the clinical management of GO with cyclosporin A. Scaling and root planing eliminated the inflammatory component of the GO, the fibrous component representing 60% of the dysmorphism. In our study, patients in the experimental group presented better results in the maxilla than the control group, while in mandible there were no significant differences.

The conversion from cyclosporin A to tacrolimus produces a resolution of GO within the first month.

In our study, no greater efficacy was proven for conventional periodontal treatment in combination with the administration of tacrolimus, in comparison with the removal of cyclosporin A in favor of tacrolimus as monotherapy for the reduction of GO.

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