Update on gingival overgrowth by cyclosporine A in renal transplants

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ABSTRACT
Severe gingival overgrowth is one of the most frequent side effects in renal transplant patients associated with assumption of cyclosporine A. Several associations with age, sex, dosage, duration of therapy or interval since transplantation have been hypothesized. The introduction of alternative immunosuppressant drugs have been suggested to permit better long-term transplant outcomes and a decrease in incidence of gingival overgrowth. The aim of the present paper is to summarize current knowledge regarding aetiology, pathogenesis and management of gingival overgrowth induced by Cyclosporine A.

Key words: *Gingival overgrowth, cyclosporine A, renal transplantation.*

RESUMEN
El sobrecrecimiento gingival severo es uno de los efectos adversos más frecuentes en los pacientes con transplante renal asociado al suministro de ciclosporina A. Se han realizado hipótesis sobre diversas asociaciones con la edad, sexo, dosis, duración de la terapia o intervalo desde el transplante. Se ha propuesto la introducción de la alternativa de drogas inmunosupresoras para permitir mejores resultados a largo plazo del transplante y la disminución en la incidencia de sobrecrecimiento gingival. El objetivo del presente estudio es resumir el conocimiento actual, observando la etiología, patogénesis y dirección del sobrecrecimiento gingival inducido por la ciclosporina A.

Palabras clave: *Sobrecrecimiento gingival, ciclosporina A, transplante renal.*

INTRODUCTION

Organ transplantation procedures necessitate the use of immunosuppressant drugs. Immunosuppressant therapy is prescribed in treatment of autoimmune diseases and prevention of organ transplants rejection. The increased use of these medications has focused attention on the specific toxicities and side-effects associated (1, 2).

Since 1965, Merrill (3) performed in human beings the renal transplant and now it is considered a routine therapy for the treatment of irreversible renal failures. After renal transplantation, it is mandatory beginning immunosuppressant therapy in order to create a condition in which lymphocytes are not active, to avoid renal transplant rejection (4).

Cyclosporine A (CsA) has been the primary tool to prevent the rejection of organ transplants. The clinical use of CsA is often complicated by several well documented side effects including gingival overgrowth (GO) (5, 6) (Table 1).

The disfiguring GO may interfere with the normal oral functions and may also cause delayed and/or ectopic eruption of teeth, impaired speech, headache appearance and difficulty in maintaining optimal oral hygiene resulting in an increased susceptibility to infections, caries, and periodontal diseases (7). Furthermore, these consequences may have a psychological impact in children and may in turn influence compliance with medical therapy.

In the last years, new drugs have been used to avoid renal transplant rejection and to limit the well known side effects. Several studies indicate 'improvement' in GO when patients use new immunosuppressant drugs, such as Tacrolimus (FK506, Prograf® Fujisawa, Japan), Rapamycin RS 61443 and Mycophenolate mofetil (MMF) (CellCept®) (8), even if their collateral effects are not still extensively reported and, for this reason, CsA is still the mostly used drug in renal transplant therapy (9,10). However, there is evidence that use of Tacrolimus causes fewer oral side-effects than CsA (8,11,12).

INMUNOSUPPRESSANT THERAPY

After renal transplant, the therapeutic schemes of immunosuppressant drugs are several: at first time, it is used to give high dose of drugs followed to a support period in which reducing dosage therapeutic till the lowest dosage possible. The protocol applied has varied from mono-therapy, (6-metilprednisolone or CsA) to a combination of two drugs (CsA and cortisone or alternatively CsA and dihydropyridine) up to the use of three drugs (CsA, cortisone and azathioprine) (9,10).

Among these drugs CsA is a non-myelotoxic immunosuppressant and its primary target is helper/inducer T lymphocytes; azathioprine is a non specific myelosuppressive commonly used together with prednisolone (triple medication), dihydropyridines are calcium-channel blocking agents used in the management of cardiovascular disorders, which have been shown to suppress cell-mediated immunity (13, 14). Dihydropyridines may have a synergistic immunosuppressant effect on CsA therapy (15) and on CsA induced suppression of T-cell proliferation (16) with the advantage of reducing the nephrotoxicity. Renal transplant patients are frequently treated with both CsA and dihydropyridine.

The increased use of immunosuppressive medication has focused attention on the specific toxicities and side-effects associated with these agents.

CYCLOSPORIN A

Cyclosporin (CsA) (Sandimmune® Novartis Pharmaceuticals Corporation, Hanover, Germany) was introduced in 1972 thanks to Borel of the Sandoz pharmaceutical company and registered in 1983. It is a lipophilic cyclic endecapeptide, isolated as an antifungal, from soil samples containing Cylindrocarpon lucidum BOOTH and Tolypocladium inflatum GAMS (fungi imperfecti) (17).

Table 1. Reported side effects of CsA.

• **Nephrotoxicity**	• **Hypertension**
• **Hepatotoxicity**	• **Biliary calculus disease**
• **Diabetes**	• **Neurotoxicity**
• **Epilepsy**	• **Hirsutism**
• **Tremors**	• **Altered bone metabolism**
• **Lingual fungiform papillae hypertrophy**	• **Gingival Overgrowth**
• **Plasmocytoma**	• **Kaposi's sarcoma**
• **Squamous cell carcinoma of the lips**	• **Cephalalgy**
• **Sinusitis**	• **Conjunctivitis**
• **Hairy-leukoplakia**	

The molecular tertiary structure results in the formation of hydrophilic immunosuppressant binding site and reduces immunosuppressant potential (18,19). CsA is variably absorbed in the gut and peak plasma concentration is reached after 3-4 hours. The drug is mostly bound to the following cells: 50% erythrocytes, 5% lymphocytes and 40% lipoproteins (20), with approximately 5% free in the plasma (7). CsA is metabolised in the liver microsomes (21), and excreted after 6 hours mainly via the bile, through the faeces (22).

In vitro and in vivo experiments indicated that CsA interferes selectively on T cell, particularly it inhibits T helper cells and it has get or no effect on T suppressor cells (23-25).

CsA inhibits selectively macrophage activation and IL-1 production, it prevents production of IL-1 receptors on T helper cells (26), inhibits IL-2 synthesis at low concentrations limiting clonal amplification of citotoxic T cell, and it inhibits their ability to respond to IL-2 (probably blocking cell surface receptors) (27).

CsA passively diffuses through cell membranes of many cells (including all peripheral blood lymphocytes and erytrocytes) and is concentrated in cytoplasm and nucleus (7).

The pharmacokinetic problems due to incomplete, unpredictable and inadequate absorption of original formulation of CsA have brought to introduction of new microemulsion formulation of CsA (Neoral), characterized to better absorption and a lower intra/inter-patient variability, permitting a improved long-term transplant outcomes (28, 29).

PATHOGENESIS

The pathogenesis of CsA-GO is probably multifactorial and still uncertain. Some studies have suggested associations between incidence-severity of GO and sex (30), age at transplantation (31, 32), duration of therapy and CsA dosage, (33-35) significant drug-related risk factors for the development of the clinical conditions (31, 32, 36-38). There is a wide intra and inter-individual variability in the susceptibility of the CsA to induce GO (CsA-GO) (range 30 to 50%) (39) and regularly it appears in more than 70% of adult transplant patients (31, 40).

It has been reported that CsA is able to alter the metabolism of human gingival fibroblasts (41) and the lamina propria extracellular components. Histologically, gingival hyperplasia is associated with an increase in the deposition of intercellular matrix, in the percentage of inflammatory cells (particularly macrophages, also known as Langerhans cells), and in the degree of tissue vascularization(42-46). This inflammatory response is increased by the presence of dental plaque, suggesting that the hyperplasia can represent a response to the bacterial toxins (47, 48).

Some studies have suggested that this type of GO is related to an individual drug or metabolite susceptibility (5) since gingival fibroblasts show an individual drug response (49). It is possible that CsA and its metabolites react with a phenotypically distinct subpopulation of gingival fibroblasts causing an increase in protein synthesis and rate of cell proliferation (50, 51). However, fibroblast heterogeneity has been demonstrated in relation to collagenase activity suggesting that CsA-GO involves an increase in the amount of collagen and extra cellular matrix formation (52) rather than an increase in the number of fibroblasts (53); this is could be a strange condition because IL-6 inhibits fibroblast proliferation (by the inhibiting of stimulatory cytokines) (54).

Morton et al. (55) found that gingival fibroblasts respond to CsA increasing IL-6 secretion, which itself enhances collagen and glycosaminoglycan synthesis. They also observed that CsA synergizes with IL-1ß to further up-regulated IL-6 secretion asserted that one of the pathogenic mechanisms underlying drug-induced GO might be enhanced secretion of IL-6 by gingival fibroblasts (55). It has been reported that gingival fibroblasts produce considerable quantity of IL-6, especially after stimulation with bacteria or other cytokines (56).

In renal transplantation patients (57) increased levels of IL-6 have been reported, (58,59), but the cellular origin of IL-6 in CsA-GO is unknown. Although immune cells such as lymphocytes and monocytes could be the source of this cytokine, it is evident that the substantial rise in IL-6 activity in renal transplant or gingival tissues of CsA-treated patients cannot be attributed to inflammatory cell infiltrates (60, 61).

In relation to phagocytosis, fibroblasts from CsA-GO showed reduced phagocyte activity in inflamed tissue, as a result of lower proportions of phagocytes (35, 62). An increased rate of synthesis coupled with a decreased rate of phagocytosis would result in an evident increased amount of essential substance and it could explain the increase of connective tissue volume in CsA-GO.

Hence, it is possible to hypothesize that those individuals treated by CsA and genetically susceptible to GO, have got an appropriate mixture of fibroblast and lymphocyte subpopulations, as being able to interact with CsA in inflamed gingival tissue, up to the well known GO clinical manifestations (63).

CSA THERAPY IN AUTOINMUNE DISORDERS AND ORAL SIDE EFFECTS

CsA is increasingly used, not only in transplantation practice but, also, in autoimmune disorders (i.e. psoriasis, systemic lupus erythematous, rheumatoid arthritis and multiple sclerosis) causing equally various side effects as in the oral cavity. In this district, the rare lingual fungiform papillae hypertrophy (LFPH), GO (64, 65), opportunistic infections, hairy leukoplakia (66, 67) and squamous cells carcinoma of the lip (67) have been repeatedly reported. Many studies have examined interaction of CsA with gingival fibroblasts, reporting a correlation between CsA effects on fibroblasts and extra-cellular components of connective lamina propria and GO; in fact, gingival fibroblasts show an individual response to the drug (68). Clinically gingival hyperplasia begins at the interdental papillae, more commonly in anterior than in posterior region, and frequently on labial than on lingual surfaces (30, 69, 70).

Hyperplasia is often limited on adherent gingiva, but it may to extend coronally and interfere with occlusion, mastication

and language, without necessarily altering the underlying periodontium. Hyperplasia origin is apparently due to many factors: age, dosage, time of CsA assumption and possible additional other drugs. CsA-GO has not been described in edentulous patients or in edentulous space (40,71), even if few authors have reported CsA-GO in edentulous patients (71-75); in these latter cases an association of the hyperplasia emerges with denture trauma or candidal infection (71).

RISK FACTORS ASSOCIATED WITH SEVERITY OF GINGIVAL OVERGROWTH

Serum and salivary concentrations, dosage of the drug, time since transplantation and assumption of drug, age, concomitant medication and oral hygiene are some the main risk factors influencing the severity of GO in renal transplantation patients.

SERUM CONCENTRATION AND DOSAGE

This point has been discussed in controversial manner: some authors have found a correlation between the dosage of CsA and development severity of GO (34, 76), while others have reported contrasting findings (7, 42,78,79). There is a general agreement that an initial threshold serum concentration is required to initiate GO and it has been suggested that the higher is the serum concentration the quicker GO develops (76).

SALIVARY CONCENTRATION

Salivary concentrations of CsA are higher in patients taking the liquid form of the drug compared to the capsule form, but salivary concentrations are poorly correlated with blood levels (80).

TIME OF ADMINISTRATION

The relationship between GO and time of administration is another controversial issue since GO has been reported both in patients taking CsA within three months (34) or more (5). But, a recent report in children indicated that only subjects taking CsA for more than three months showed in all cases GO (81).

DURATION

Duration of CsA therapy has been reported to increase the chance to have GO. Recently, a significant inverse correlation between periodontal status and duration of therapy has been reported, thus the negative effects of the drug could spontaneously decrease over time (82).

AGE AND SEX

Prevalence and severity of GO has been reported to be significantly higher in children in comparison to the adults undergoing organ transplants. (79, 83). The immature fibroblasts, probably, are more sensitive to the effect of CsA (84, 85), so the increase GO in adolescents can be due to an interaction between circulating androgens, estrogens and gingival fibroblasts. Studies seem to suggest that children, especially adolescents and females may be more susceptible to this undesirable effect than adults (42, 86) The high-level of sexual hormones found in patients of this age produce an active metabolite (5 alpha-dihydrotestosterone) that acts on a subpopulation of gingival fibroblasts as being to the increase collagen synthesis and/or to decrease the collagenase production (87). In addition to the potential effect of hormones in adolescence, there is evidence that GO is influenced by orthodontic appliances which may irritate the soft tissues and act as a plaque trap thereby increasing the GO (88).

COMBINATIONS OF MEDICATIONS ASSOCIATED WITH GINGIVAL OVERGROWTH

The most common combination of drugs that cause GO is CsA and nifedipine. Nifedipine is used habitually to treat hypertension which may be primary or secondary to CsA nephrotoxicity (36, 89). A significant increase in the incidence of GO has been described in renal transplant patients taking nifedipine and CsA compared with those taking CsA alone (51 per cent vs 8 per cent) (90).

GENETIC PREDISPOSITION

The role of individual susceptibility to GO has recently attracted much attention. Several studies (32, 37, 38) have described slight disease association between HLA alleles (A19, A24 and DR-2), and a possible protective effect of HLA-B37 and DR-1. The selectivity of the overgrowth to particular regions of the mouth and only in some patients, suggested a genetic predisposition that may interact with the local environment resulting in GO (39).

ORAL HYGIENE

It is well known that dental plaque is composed of an aggregation of micro organisms deposited on the tooth surfaces and it is able to begin inflammatory changes in the gingival tissues. Mediators of the inflammatory response cause the changes in gingival tissues (91). These inflammatory changes may increase the interaction between CsA and fibroblasts leading to changes in connective tissue turnover. The improvement of general standard of oral hygiene can reduce GO resolving the inflammatory component plaque induced. In a longitudinal study, the effect on GO-CsA of a given oral hygiene program was examined in adult transplant patients (92): both the oral hygiene and the control group registered a significant gingival change, however, the degree of GO was less marked in the group with oral hygiene program.

Although the role of plaque has not been clearly defined consistently with other several authors (93-96), the hyperplastic tissue tends to aid plaque accumulation and to inhibit plaque removal, increases the gingival inflammation.

MANAGEMENT OF GINGIVAL OVERGROWTH

Different therapeutic approaches for GO management have been proposed. The use of specific oral hygiene programs, surgical intervention and/or alternative pharmacological therapy have been reported.

Severe oral hygiene measures may reduce the degree of GO, but they do not inhibit its development.

The need for surgical treatment to be carefully assessed. Surgery is normally performed for cosmetic/aesthetic requests before any functional need is showed. In cases where drug therapy must be continued for several years, psychosocial support need to be considered with the purpose to reduce the frequency and extension of surgical interventions.

Reduction in the dose of CsA has been shown to be beneficial versus GO but, frequently, the nature of organ transplants does not permit an alternative therapy or dose reduction (97).

When possible, alternatively to CsA, some patients can use other immunosuppressant drugs such as tacrolimus (FK506), azathioprine and rapamycin that may offer some hope not reporting GO associated. There is evidence to support the use of Tacrolimus over CsA since it has shown to cause fewer oral side-effects than CsA (11, 12), even if tacrolimus may stimulate formation of cyst in anterior site of mouth and increase infections by Human Papilloma Virus, xerostomia, and oral ulcers (67). Tacrolimus/FK 506, a macrolide molecule, acts primarily on CD4+ T helper lymphocytes by inhibiting the production of lymphokines, which are required for cell growth and differentiation, principally of IL-2, at the transcriptional level (98). It has also been suggested that the elimination of CsA and its replacement of Tacrolimus removes the up regulation of CsA-induced essential polypeptide growth factors, which are important mediators in development of GO (99).

CONCLUSION

CsA is an immunosuppressant used widely for its rejection-preventing power in human organ of transplantation (7, 100). One of the side effects associated with CsA treatment is GO; CsA-GO is generally associated with acute or chronic inflammation due to plaque accumulation (101, 102), reported dosage of CsA (103), presence of local gingival inflammation and gingivitis as independent predictors of the extent/severity of GO. An individual genetic susceptibility can be more or less responsible of the clinical manifestation of GO.

The present paper is drawn to underline the etiological relationships and clarify some important aspects on the risk factors responsible of CsA-GO in renal transplantation patients. In the future, dosage reduction and/or replacement of CsA with alternative efficacious pharmacological therapies to the CsA will undoubtedly taken into account in order to improve the oral health in these patients.

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