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Cyclosporin, Nifedipine and gingival hyperplasia: a randomized controlled study

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Abstract Nifedipine increases the frequency and severity of gingival hyperplasia associated with CyA therapy in renal transplant recipients and this effect appears to be independent of whole-blood CyA levels. De novo malignancies have been reported arising in areas of gingival hyperplasia, in a group already at high risk of malignancy. Patients receiving CyA and nifedipine should receive advice regarding the need for strict oral hygiene to control the initial development of gingival hyperplasia, with severe cases being promptly referred for gingivectomy and histological examination.

Key words Cyclosporin A
Nifedipine · Gingival hyperplasia
Renal transplantation

Introduction

Cyclosporin A (CyA) has been widely used as an immunosuppressant since its inhibitory effect on lymphocyte populations was reported by Borel in the 1970s and was first used clinically by Calne in renal allograft recipients in 1978. Gingival hyperplasia was reported as being amonst the many side effects of CyA by Starzl in 1980. It has been reported to occur in 8–80% of cases [3]. Nifedipine, a calcium-channel-blocking drug widely used as an antihypertensive agent, has been reported to cause gingival hyperplasia in renal transplant recipients both independently and in conjunction with CyA. A cumulative effect has been suggested by a retrospective study of nifedipine and CyA in renal transplant patients [4]. There have been three cases of malignancy reported developing in areas of gingival hyperplasia in renal transplant patients, one squamous cell carcinoma and two Kaposi's sarcomata [2, 5]. This clearly makes investigation of gingival hyperplasia very important in this already vulnerable group. The aim of this study was to prospectively examine the development of gingival hyperplasia in a randomized clinical trial of high- and low-dose CyA in conjunction with nifedipine.

Patients and methods

At the time of renal transplantation patients were randomly allocated to one of three immunosuppressive regimens. Group A ($n = 15$) received an initial cyclosporin dose of 17 mg/kg per day reducing by 2 mg/kg per week to 7 mg/kg per day. Group B ($n = 17$) received regimen A plus nifedipine. Group C ($n = 17$) received an initial cyclosporin dose of 10 mg/kg per day reducing by 2 mg/kg per week to 4 mg/kg per day, plus azathioprine 1 mg/kg per day, adjusted to avoid leucopenia. All groups received an identical reducing steroid regimen adjusted for body mass. Calcium channel blockers of all types were avoided in groups A and C, with non-calcium channel blocking drugs used where necessary. Edentulous patients were excluded from the analysis as they do not develop gingival hyperplasia.

Patients were examined 3 months post-transplant for signs of gingival hyperplasia, using the system of Matarasso et al [1] and were graded as none = 0, mild = 1, moderate = 2, and severe = 3. Whole-blood CyA levels were measured using HPLC.

Table 1 Comparison of degree of gingival hyperplasia and CyA levels with different Immunosuppressive regimens

* $P < 0.001$ vs groups A and B,
** $P < 0.001$ vs group B,
*** $P < 0.05$ vs group B

	Number	CyA level (ng/ml)	None/mild (0/1)	Moderate/severe (3/4)
Group A	15	388	15	0**
Group B	17	378	8	9
Group C	17	208*	14	3***

Results

It was found that patients with grade 1 hyperplasia were easily controlled by simple oral hygiene, whereas patients with grade 2 and 3 hyperplasia were more likely to need formal gingivectomy, and would be more at risk of developing malignancy. Table 1 shows the mean whole-blood CyA levels for each treatment group, and the numbers of patients with gingival hyperplasia, by grade. The mean whole-blood CyA level did not appear to be related to the grade of hyperplasia and was not significantly different between grades (grade 0 = 391 ng/ml, grade 1 = 265 ng/ml, grade 2 = 283 ng/ml, grade 3 = 239 ng/ml).

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