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Incidence of tacrolimus-induced gingival overgrowth in the absence of calcium channel blockers: a short-term study

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Abstract

Aim: The aim of this study was to determine the incidence and severity of gingival overgrowth (GO) induced by tacrolimus (Tcr) compared with ciclosporin A (CiA) in the absence of calcium channel blockers (CCB) in renal transplant recipients.

Methods: Forty patients (20 Tcr and 20 CiA) were evaluated before and 30 and 90 days after kidney transplantation. Demographic (age, gender) and periodontal parameters were recorded for all patients. Patients taking CCB at any time during the study were excluded from the investigation.

Results: The mean GO score was significantly lower ($p = 0.014$) in the Tcr group (6.4%) compared with the CiA group (17.9%) after 90 days of immunosuppressive therapy. At 90 days post-transplant, clinically significant GO was observed in four patients of the CiA group and in two of the Tcr group. This difference was not statistically significant (0.66).

Conclusion: No significant difference in the incidence of clinically significant GO was observed between the CiA and Tcr groups up to 90 days of immunosuppressive therapy.

Key words: ciclosporin; gingival overgrowth; periodontal diseases; tacrolimus

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Gingival overgrowth (GO) induced by immunosuppressive agents has been studied over decades. This disorder can affect all regions of the mouth but is more evident in inter-papillary areas of the anterior region and more frequent on the buccal aspect (Rateitschak-Plüss et al. 1983, Adams & Davies 1984, Somacarrera et al. 1994, Thomason et al. 2005). In some cases, this abnormality may extend to the dental crown and interfere with occlusion, mastication and phonetics (Friskopp & Klintmalm 1986). In more severe cases, GO may cause aesthetic and psychological problems (James et al. 2000).

The main immunosuppressive agents associated with the induction of GO are ciclosporin A (CiA) and tacrolimus (Tcr). Tcr and CiA present some similar side effects such as nephrotoxicity, neurotoxicity and induction of a diabetic state (Starzl et al. 1990). However, studies comparing GO related to the use of Tcr and CiA have yielded divergent results. Some reports of clinical cases have associated the occurrence of this side effect with the use of Tcr (Adams & Famili 1991), although at a lower frequency than that attributed to the use of CiA (Shapiro et al. 1994, Asante-Korang et al. 1996, James et al. 2001, Oettinger-Barak et al. 2001, Ellis et al. 2004). In contrast, other studies have suggested that Tcr may not provoke GO, thus representing an important differential property for its indication (Asante-Korang et al. 1996, Cox & Freese 1996, Shield et al. 1997).

The prevalence of GO in immunosuppressed patients using CiA ranges from 20% to 35%, with the highest incidences being related to the concomitant use of calcium channel blockers (King et al. 1993, Thomason et al. 1993, Somacarrera et al. 1994). The prevalence of Tcr-induced GO is approximately 14% (Ellis et al. 2004, Thomason et al. 2005), and the concomitant use of calcium channel

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blockers can also increase the severity of this condition.

The objective of this study was to compare the incidence and severity of GO associated with the administration of the immunosuppressive drugs Tcr and CiA in renal transplant patients in the absence of calcium channel blockers.

Material and Methods

Study design and sample

A longitudinal study was conducted at Hospital do Rim e Hipertensão, Universidade Federal de São Paulo, between January 2003 and October 2005. The study was approved by the Ethics Committee of the institution and all participants signed a free informed consent form.

Included in the study were subjects of both sexes older than 18 years, who had at least six of the eight anterior teeth in each arch and presented no clinical or radiographic signs of periodontitis (Armitage 1999). The maximum interval between periodontal assessment and transplant surgery was 15 days in order to guarantee the absence of any change in the parameters evaluated. Smokers and/or diabetic patients and patients presenting some type of GO during the pre-transplant period were excluded from the study. Patients using one of the following drugs were also excluded nifedipine, diltiazem, verapamil, phenytoin, sodium valproate and azithromycin.

Sixty-seven renal transplant candidates were initially evaluated. Of these, 12 withdrew from the study after the initial assessment and 10 other patients were excluded because they received nifedipine after transplantation. In two cases, the immunosuppressive medication was altered during the study period. Three other subjects did not appear for periodontal assessment during the indicated period. Thus, 40 subjects undergoing kidney transplantation participated in all clinical assessments and received two different immunosuppressive protocols after surgery as described below.

All participants were evaluated at three time points: before kidney transplantation (pre-transplant period) and 30 and 90 days after transplantation.

Immunosuppression protocols

The immunosuppression protocols used after kidney transplantation were instituted and monitored by the medical team, as shown in Tables 1 and 2. The CiA group consisted of 20 subjects maintained on a triple immunosuppression protocol of CiA, azathioprine and a corticosteroid, and the Tcr group consisted of 20 subjects receiving Tcr, azathioprine and a corticosteroid. All patients also received a combination of trimethoprim and sulfamethoxazole after transplantation during the 90 days of the study.

Clinical periodontal assessment

Clinical assessment was performed by a single trained and calibrated examiner. Assessment of measurement reproducibility used replicate periodontal examinations, conducted at the beginning and during the study. Measurement reproducibility was calculated by intra-class correlation coefficient (ICC) for the variables distance from the cemento-enamel junction to the gingival margin (CEJ–GM), probing depth (PD) and GO. Reproducibility of the variables plaque index (PI) and bleeding on probing (BOP) was calculated by weighted κ. Agreement between replicate measurements was high (ICC $\geqslant$ 0.85; weighted $\kappa \geqslant 0.85$) for all variables.

The clinical parameters were measured with a millimeter-graded manual periodontal probe (Hu-Friedy, Chicago, IL, USA; PCPUNC No. 15) in six of the most anterior teeth of the dental arch and at six sites per tooth (distal–buccal, central–buccal, mesial–buccal, distal–lingual, central–lingual and mesial–lingual). The following clinical parameters were determined: CEJ–GM, PD, CAL, PI of Silness & Löe (1964), BOP and GO. In all examinations, the examiner was blinded to the patient's drug regime.

GO was analysed by visual examination of the buccal and lingual papillae of the six most anterior teeth of the upper and lower arch. A score ranging from 0 to 5 was attributed to each papilla according to the quantity of GO both in the horizontal and vertical axes. Thus, a total of 20 papillae were analysed per patient, corresponding to a maximum score of 100, which is expressed as percentage. Patients showing a score $\geqslant$30 were classified as presenting clinically significant GO. This cutoff value was based on previous studies (Seymour & Jacobs 1992, Thomason et al. 1993). The same clinical measurements were repeated 30 and 90 days after transplantation. All patients received thorough scaling and root planing and oral hygiene instruction before transplant surgery. In all subsequent assessments, the patients received renewed motivation regarding oral hygiene, and prophylaxis and scaling were performed in the presence of calculus.

Statistical analysis

First, means of the variables CEJ–GM, PD, CAL, PI and BOP were calculated per patient. The GO index is reported as percentage.

Mean age, CEJ–GM, PD, CAL, PI, BOP and GO were compared between the CiA and Tcr groups before and 30 and 90 days after kidney transplantation. ANOVA for repeated measures was used to compare means between groups along

Table 1. Serum concentration of ciclosporin according to post-transplant periods

Post-transplant period	Ciclosporin serum concentration	
	range (ng/ml)	mean ± SD
0–30 days	200–400	297.05 ± 41.25
31–90 days	150–300	231.00 ± 38.98
After 90 days	100–200	147.35 ± 16.97

Table 2. Serum concentration of tacrolimus according to post-transplant periods

Post-transplant period	Tacrolimus serum concentration	
	range (ng/ml)	mean ± SD
0–15 days	15–20	16.65 ± 1.46
16–30 days	10–15	12.40 ± 1.39
31–90 days	8–15	10.35 ± 2.27
After 90 days	5–15	8.80 ± 2.41

time. The Tukey test was applied to detect differences between groups. When the distribution was not normal or when the variances were not homogenous, the non-parametric Mann–Whitney test was used to compare means between the two groups at each time interval, and the non-parametric Friedman's test was applied to determine changes in each group along time. The χ^2 test was used to determine the association between group and GO index at the three time points studied. The α level for rejection of the null hypothesis was set at 5% for all tests.

Results

Forty subjects aged 21–60 years (mean ± SD, 39.3 ± 11.7 years) participated in the study. Table 3 shows that the two groups were homogenous in terms of age ($p = 0.98$) and gender ($p = 0.74$). Table 4 shows the alterations in the clinical variables over time.

At the beginning of the study, the CiA and Tcr groups presented a mean gingival recession of 0.36 and 0.19 mm, respectively. No significant change over time was observed in the Tcr group. In the CiA group, a significant mean reduction of 0.23 mm in recession was observed between the pre-transplant period and 90 days after transplantation ($p = 0.009$). There was no difference between groups at any time studied.

Mean PD did not differ significantly between the two groups at any time point studied. No significant change over time was observed in the CiA ($p = 0.10$) or Tcr group ($p = 0.09$).

ANOVA revealed a significant change in CAL over time in the two groups ($p = 0.01$). The CiA group presented a reduction in CAL of 0.09 mm, whereas a reduction of 0.04 mm was observed in the Tcr group, with no difference between groups.

A significant reduction in PI scores of 0.3 and 0.4 was observed in the CiA ($p = 0.001$) and Tcr ($p = 0.005$) groups, respectively, but there was no difference between groups.

BOP was reduced by 4.2% in the CiA group and by 11.7% in the Tcr group, with this reduction being significant in both groups (ANOVA, $p < 0.001$). No difference was observed between groups.

Comparison of the GO index between the two groups showed a significant increase in the Tcr ($p = 0.007$) and CiA ($p < 0.001$) groups. In the CiA group, the Student–Newman–Keuls multiple comparisons test revealed a significant difference between the pre-transplant period and 30 days post-transplant ($p = 0.006$), between the pre-transplant period and 90 days post-transplant ($p < 0.001$), and between 30 and 90 days post-transplant ($p = 0.0002$). In the Tcr group, a significant difference was observed between the pre-transplant period and 90 days post-transplant ($p = 0.049$). Mean GO was significantly lower in the Tcr group 30 days ($p = 0.03$) and 90 days ($p = 0.014$) after transplantation.

None of the patients of the CiA or Tcr group presented GO before kidney transplantation (Table 5). At 30 days post-transplant, clinically significant GO was observed in two patients receiving CiA but in none of the patients receiving Tcr. No significant association was observed between clinically significant GO and group ($p = 0.48$) at 30 days post-transplant. At 90 days post-transplant, clinically significant GO was observed in four patients of the CiA group and in two of the Tcr group but there was also no significant association between clinically significant GO and group at this time point ($p = 0.66$).

Individuals presenting clinically significant GO at 90 days post-transplant ($n = 6$) were compared with the other patients ($n = 34$), regardless of the immunosuppressive agent (Table 6). It was observed that subjects with clinically significant GO presented

Table 3. Demographic and clinical data of the patients studied

	CiA ($n = 20$)	Tcr ($n = 20$)	p
Age (years)			
Mean ± SD	39.3 ± 11.7	39.4 ± 12.9	0.98
Range	22–57	21–60	
Gender			
Male	8 (40.0%)	11 (50.0%)	0.74
Female	12 (60.0%)	9 (45.0%)	

CiA, ciclosporin A; Tcr, tacrolimus.

Table 4. Comparison of the periodontal variables CEJ–GM, PD, CAL, BOP, PI and GO between the groups receiving ciclosporin A (CiA) and tacrolimus (Tcr)

	Pre-transplant	30 days	90 days	p
CEJ–GM				
CiA ($n = 20$)	0.36 ± 0.51	0.26 ± 0.52	0.13 ± 0.89	0.009*
Tcr ($n = 20$)	0.19 ± 0.32	0.19 ± 0.34	0.13 ± 0.34	0.10
p (Mann–Whitney)	0.36	0.84	0.73	(Friedman)
PD				
CiA ($n = 20$)	1.87 ± 0.26	1.87 ± 0.33	2.05 ± 0.89	0.10
Tcr ($n = 20$)	1.83 ± 0.44	1.78 ± 0.39	1.85 ± 0.35	0.09
p	0.62	0.58	0.62	(Friedman)
CAL				
CiA ($n = 20$)	2.23 ± 0.63	2.13 ± 0.54	2.14 ± 0.54	0.01*
Tcr ($n = 20$)	2.02 ± 0.60	1.98 ± 0.46	1.98 ± 0.45	(ANOVA)
p (Tukey)	0.97	0.99	0.99	
BOP (%)				
CiA ($n = 20$)	30.5 ± 12.7	28.1 ± 15.3	26.3 ± 14.7	<0.001*
Tcr ($n = 20$)	35.2 ± 22.8	27.3 ± 16.6	23.5 ± 10.9	(ANOVA)
p (Tukey)	0.99	0.99	0.99	
PI				
CiA ($n = 20$)	1.2 ± 0.6	0.9 ± 0.5	0.9 ± 0.5	0.001*
Tcr ($n = 20$)	1.3 ± 0.7	1.0 ± 0.4	0.9 ± 0.2	0.005*
p (Mann–Whitney)	0.94	0.12	0.69	(Friedman)
GO				
CiA ($n = 20$)	0.0 ± 0.0	8.9 ± 14.9	17.9 ± 18.8	<0.001*
Tcr ($n = 20$)	0.0 ± 0.0	0.0 ± 0.0	6.4 ± 11.9	0.007*
p (Mann–Whitney)	1.00	0.03*	0.014*	(Friedman)

Values are means ± SD.

CEJ–GM, distance between the cementoenamel junction and gingival margin; PD, probing depth; CAL, clinical attachment level; BOP, bleeding on probing; PI, plaque index; GO, gingival overgrowth; SD, standard deviation.

*Significant difference at the 5% level.

significantly greater CEJ–GM mean ($p = 0.001$), PD mean ($p = 0.002$), PI mean ($p = 0.001$) and BOP mean ($p = 0.002$) at 90 days post-transplant, when compared with the other individuals. Tables 7 and 8 show the serum concentration of CiA and Tcr according to post-transplant periods, in individuals presenting clinically significant GO at 90 days after transplant and in individuals with no clinically significant GO.

Discussion

The Tcr group presented a mean GO of 6.4% at 90 days post-transplant. In contrast, in the CiA group the mean GO was 8.9% at 30 days post-transplant and increased to 17.9% after 90 days. The mean GO was significantly lower in the Tcr group than in the CiA group at 30 days ($p = 0.03$) and 90 days ($p = 0.014$). These results are similar to those reported by Ellis et al. (2004) who observed a mean GO of 14.1% in the group receiving Tcr and of 22.4% in the group receiving CiA. In contrast, the mean GO observed here was lower than that reported by Thomason et al. (1993) who found a mean overgrowth of 20.6% in the group receiving CiA. One possible explanation for the difference in these results is that in this study all patients received triple immunosuppressive therapy including the main immunosuppressive agent (CiA or Tcr), azathioprine and a corticosteroid (methylprednisolone and prednisolone). According to Thomason et al. (2005), the use of azathioprine and corticosteroids may reduce the CiA or Tcr dose and thus result in a lower frequency of GO.

At 30 days post-transplant, clinically significant GO was only observed in two (10%) patients of the CiA group and in none of the Tcr group. After 90 days, four (20%) subjects of the CiA group and two (10%) of the Tcr group presented this gingival change. No significant difference in the incidence of GO was observed between the CiA and Tcr groups at either time point. Ellis et al. (2004) also found no significant difference between groups receiving CiA and Tcr ($p = 0.053$), although the authors considered this difference to be marginally significant. Methodological differences between studies might be one explanation for the different results. Ellis et al. (2004) conducted a cross-sectional study in which no rigorous control of the dental biofilm was performed, a fact that might have resulted in more severe GO due to inflammation. In addition, the mean duration of immunosuppressive therapy was 31 months in the Tcr group and 42 months in the CiA group. In contrast, in this prospective study adequate control of the dental biofilm was performed and the duration of immunosuppressive therapy was only 3 months. According to Daley et al. (1986) and Somacarrera et al. (1994), evident clinical signs of GO are observed within the first 90 days of immunosuppressive therapy, but this alteration only stabilizes after 12 months of therapy. However, in some subjects GO may occur after this period, thus resulting in a greater difference between the CiA and Tcr groups.

A high proportion of renal transplant recipients also use calcium channel blockers (nifedipine, diltiazem, verapamil or amlodipine) to control arterial

Table 5. Distribution of patients according to group and the occurrence of clinically significant gingival overgrowth

	Incidence of clinically significant overgrowth *n* (%)		
	pre-transplant	30 days post-transplant	90 days post-transplant
Ciclosporin ($n = 20$)	0 (0)	2 (10)	4 (20)
Tacrolimus ($n = 20$)	0 (0)	0 (0)	2 (10)
Total ($n = 40$)	0 (0)	2 (5)	6 (15)

Table 6. Comparison of the variables age, CEJ–GM, PD, CAL, BOP, PI and GO between individuals presenting clinically significant gingival overgrowth at 90 days after transplant (CS) and individuals with no clinically significant gingival overgrowth (NCS)

	CS ($n = 6$) mean ± SD	NCS ($n = 34$) mean ± SD	*p*
Age (years)	41.8 ± 10.9	38.9 ± 12.5	0.98 (*t*-test)
CEJ–GM pre-transplant	0.26 ± 0.37	0.27 ± 0.44	0.92 (*t*-test)
CEJ–GM 30 days	− 0.05 ± 0.23	0.27 ± 0.43	0.08 (*t*-test)
CEJ–GM 90 days	− 0.62 ± 1.05	0.26 ± 0.48	0.001 (MW)*
PD pre-transplant	1.96 ± 0.46	1.82 ± 0.34	0.38 (*t*-test)
PD 30 days	2.07 ± 0.53	1.78 ± 0.30	0.06 (*t*-test)
PD 90 days	2.71 ± 0.29	1.82 ± 1.49	0.002 (MW)*
CAL pre-transplant	2.22 ± 0.75	2.10 ± 0.54	0.63 (*t*-test)
CAL 30 days	2.02 ± 0.37	2.06 ± 0.52	0.85 (*t*-test)
CAL 90 days	2.09 ± 0.46	2.06 ± 0.51	0.89 (*t*-test)
BOP pre-transplant	0.41 ± 0.19	0.31 ± 0.08	0.20 (*t*-test)
BOP 30 days	0.38 ± 0.12	0.25 ± 0.15	0.07 (*t*-test)
BOP 90 days	0.38 ± 0.10	0.22 ± 0.11	0.002 (*t*-test)*
PI pre-transplant	1.53 ± 0.64	1.19 ± 0.48	0.22 (*t*-test)
PI 30 days	1.08 ± 0.24	0.92 ± 0.46	0.42 (*t*-test)
PI 90 days	1.30 ± 0.58	0.77 ± 0.29	0.001 (MW)*

*Significant difference at the 5% level.

CEJ–GM, distance between the cementoenamel junction and gingival margin; PD, probing depth; CAL, clinical attachment level; BOP, bleeding on probing; PI, plaque index; GO, gingival overgrowth; MW, Mann–Whitney test.

Table 7. Serum concentration of ciclosporin according to post-transplant periods and comparison between individuals presenting clinically significant gingival overgrowth at 90 days after transplant (CS) and individuals with no clinically significant gingival overgrowth (NCS)

Post-transplant period	Ciclosporin serum concentration	
	CS ($n = 4$)	NCS ($n = 16$)
	mean ± SD	mean ± SD
0–30 days	297.25 ± 48.47	297.00 ± 41.03
31–90 days	223.75 ± 49.89	232.81 ± 37.54
After 90 days	151.25 ± 21.37	146.37 ± 16.33

Table 8. Serum concentration of tacrolimus according to post-transplant periods and comparison between individuals presenting clinically significant gingival overgrowth at 90 days after transplant (CS) and individuals with no clinically significant gingival overgrowth (NCS)

Post-transplant period (days)	Tacrolimus serum concentration	
	CS ($n = 2$) mean ± SD	NCS ($n = 18$) mean ± SD
0–15	19.00 ± 0.41	16.38 ± 1.28
16–30	11.00 ± 1.41	12.55 ± 1.33
31–90	12.00 ± 1.41	10.16 ± 2.30
After 90	10.50 ± 0.70	08.61 ± 2.47

hypertension. Previous studies have shown that the use of calcium channel blockers alone or in combination with CiA or Tcr is related to an increased prevalence and severity of GO (Ellis et al. 2004, Thomason et al. 2005). To prevent their influence on possible gingival tissue alterations, the use of these drugs was an exclusion criterion in this study. Triple immunosuppression protocols (three immunosuppressive agents) consisting of azathioprine, a corticosteroid (methylprednisolone and prednisolone) and the main agent, i.e., CiA or Tcr, were used in this study. According to Seymour et al. (1987), neither azathioprine nor corticosteroids are associated with the occurrence of GO. This fact may also explain the lower incidence and severity of GO in the patients of the study.

The role of the dental biofilm in the aetiology of GO has not been well defined. Daley et al. (1986) demonstrated that the presence of a biofilm was associated with gingival overgrowth, but little is known about the relationship between the amount of plaque and the severity of gingival overgrowth. McGaw et al. (1987) suggested that the biofilm might be a local reservoir of CiA, which slowly releases the drug through salivary stimuli. The authors also observed a higher bacterial PI in patients with gingival overgrowth. In this study, both groups demonstrated significant reductions in PI, which took place between the pre-transplant period and 30 days post-transplant and between the pre-transplant period and 90 days post-transplant. However, no significant difference between groups was observed at any time during the study. Despite the reduction in PI, GO was detected in both groups. Nevertheless, 90 days post-transplant, subjects presenting clinically significant GO presented a greater PI mean (1.30) than the other individuals (PI mean = 0.77), and the difference was significant ($p = 0.001$). These results should be analysed with care, as no multivariate analysis and statistical modelling could be used due to the small sample size.

With respect to BOP, a significant reduction was only observed in the Tcr group between the pre-transplant period and 30 days post-transplant ($p = 0.001$) and between the pre-transplant period and 90 days post-transplant ($p < 0.001$), in agreement with the study of Somacarrera et al. (1994). A reduction in BOP is related to adequate biofilm control and to the use of antimicrobial (trimethoprim and sulphamethoxazole) and anti-inflammatory (methylprednisolone and prednisolone) drugs, with these drugs inhibiting bacterial proliferation as well as inflammation. Some studies reported that patients treated with immunosuppressive agents presented fewer signs of gingival inflammation than untreated patients (Schuller et al. 1973, Kardachi & Newcomb 1978). It should be emphasized that in this study all patients received instructions about oral hygiene and were submitted to rubber cup and pumice prophylaxis and calculus removal in the three evaluations. Regarding the fact that a significant reduction of BOP was only observed in the Tcr group, the most likely explanation is that in this group the frequency of GO was lower, thus facilitating adequate biofilm control, compared with the CiA group.

In this study, the sample size was relatively small and one should therefore be cautious about applying any conclusions to the whole population. In this sample, GO was observed in patients receiving both Tcr and CiA for 90 days. The severity of overgrowth in those patients taking Tcr was significantly less than for those taking ciclosporin. The incidence of clinically significant GO was also less in the Tcr group although this difference failed to reach statistical significance, which may be attributable to the small sample size.

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Clinical Relevance

Scientific rationale for the study: Tcr is a recent immunosuppressive agent. Few data regarding the incidence of GO associated with the use of Tcr in the absence of calcium channel blockers are available in the literature.

Principal findings: The severity of GO associated with the use of Tcr was significantly lower than that induced by ciclosporin A. No significant difference in the incidence of clinically significant GO was observed between groups.

Practical implications: Tcr seems to be a good alternative, with respect to the oral condition, for transplant recipients who require immunosuppressive therapy.