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RESEARCH ARTICLE

Evaluation of Effects of Different Immunosuppressant Agents on Gingival Overgrowth

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ABSTRACT

Background: The purpose of this study is to evaluate the effects of different immunosuppressant agents on gingival overgrowth.

Materials and methods: About 60 patients medicated with cyclosporin A (CsA) and 40 patients with tacrolimus (TcR) were recruited in the study. Periodontal examination (PI, GI, PBI, PPD, GO) was carried out only for maxillary and mandibular anterior teeth. Pharmacologic variables, such as daily dosage of immunosuppressant agents, TcR/CsA whole blood level were recorded.

Results: In the group medicated with CsA, 10 patients had clinically significant GO, while none of the patients medicated with Tac had clinically significant GO. Significant differences were observed for periodontal parameters (PI, GI, PBI, PPD), post-transplant period, percentage of GO. In CsA group, significant difference was detected for periodontal parameters, percentage of GO and daily glucocorticoid dosage between responders and nonresponders.

Conclusion: The results from our study show that GO does not occur in patients medicated with TcR, although TcR shares same mechanism with CsA.

Keywords: Cyclosporin-A, Tacrolimus, Gingival overgrowth, Immunosuppressant, Transplantation.

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INTRODUCTION

Renal transplantation is the best therapeutic approach for most subjects with end-stage renal diseases. Immunosuppressive drugs, to prevent the rejection of transplanted organs, have increased the success of organ transplant surgeries.[1] However, a variety of side effects were also observed including nephrotoxicity,[2] the induction of the diabetic state, neurotoxicity[3] and gingival overgrowth (GO).[2,4-6]

Gingival overgrowth is characterized by an increase in gingival volume that is usually located in the gingival papillae without extending beyond the mucogingival junction.[2,7,8] Sometimes, this alteration may extend to the dental crown and interfere in the occlusion, mastication, and phonetics of individuals.[6]

Tacrolimus (TcR) was introduced as an immunosuppressive agent for organ transplants in 1987 and may be an excellent alternative to cyclosporin A (CsA).[7] Tacrolimus has similar side effects compared to those of CsA, but, when GO is concerned, the results appear to differ. Some studies associated the occurrence of GO with the use of TcR,[8] although at less frequency than with CsA.[7,9] In contrast, other studies[5,6] suggested that TcR is not associated with GO. The prevalence of GO induced by CsA ranges from 20 to 35%, and the high incidence could be related to the concomitant use of calcium channel blockers.[10-12] The prevalence of GO induced by TcR is ~14%,[6,10] and the concomitant use of calcium channel blockers also leads to an increase in the severity of this condition.[6,7]

The aim of this longitudinal study is to compare the incidence and severity of GO associated with the administration of immunosuppressive drugs, such as CsA and TcR, absence of calcium channel blockers in patients who underwent renal transplantation (RT) and to investigate the effects of potential risk variables associated with GO on these groups of subjects.

MATERIALS AND METHODS

Study Population

A hundred of patients with renal transplantation (38 females and 62 males) and at least 3 months postrenal transplant period under an immunosuppressive therapy based on CsA or TcR (CsA group n = 60, TcR group n = 40) were recruited. Patients' years of age were 36.19 ± 10.09 [mean ± standard deviation (SD)]. A study was conducted at the Ankara Etlik Ihtisas Hospital's Transplantation Clinic and Başkent University Transplantation Clinic between 2004 and 2006. The study was approved by

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the Ethical Committee for the use of human subjects in research, Ankara University, Faculty of Dentistry (No. 75, on Dec 9, 2004).

All subjects in this study of both sex ≥18 years. The following inclusion criteria were adopted: (1) At least 3 months postrenal transplant period under an immunosuppressive therapy, (2) a minimum of six of the 12 most anterior teeth in the upper or lower dental arches. Exclusion criteria were as follows: (1) Smokers and/or patients with diabetes, pregnancy, lactation period. (2) Patients who used drugs, such as calcium canal blockers, phenytoin, sodium valproate and medicated antibiotics, such as azithromycin 3 months before the examination. (3) Patients who had a nonsurgical periodontal treatment during the previous 6 months; surgical periodontal treatment over the previous 12 months.

Medical and Pharmacological Variables

Medical and pharmacological data were obtained from each subject's medical records. As part of long-term management, transplant recipients were screened regularly for whole blood and serum concentrations of the main immunosuppressive agent. Data from the most recent assessment, usually on the last medical examination (0-30 days, range of time between medical exam and study visit), were recorded. Gender, age, body weight, donor type, time since transplant, main immunosuppressive agent dosage and serum level, creatinine level as well as the use of prednisone, azathioprine, and mycophenolate mofetil (MMF) were used in the analysis. Patients' medical records were thoroughly examined and data were confirmed (or updated when pertinent) by the organ transplant medical group.

Clinical Parameters assessed

After the examination of patients' medical records and after applying exclusion and inclusion criterion, subjects were scheduled for gingival evaluation. Gingival evaluation was performed by a single-trained and calibrated examiner (AA) who was blinded to each patient's identity, medical history, and immunosuppressive regimen. Examiner calibration was performed at the beginning of the study and repeated 1 month later to determine intra-examiner reliability. For this purpose, papillary bleeding index (PBI) and GO scores of 10 subjects were evaluated. All nonweighted k scores were >0.92 and intra-class correlation coefficients were >0.90.

Clinical parameters were measured with a millimeter-graded manual periodontal probe[†] in six of the most anterior teeth[13,14] in the dental arch and at four sites per tooth (distal, mid-buccal, mesial, mid-lingual). The following clinical parameters were determined: Probing pocket depth (PPD), the PBI of Saxer Mühlemann,[15] the plaque index (PI) of Silness and Loe,[16] the gingival index (GI) of Löe Sillness[17] and GO. The gingival overgrowth index (GOI) was adapted from Seymour et al[18] and was recorded in the vestibular, palatine, and lingual papillae of the teeth of each individual. Each papilla received a score that ranged between 0 and 5, depending on the degree of overgrowth in both the horizontal and vertical axes. Therefore, a total of 20 papillae (10 maxillary and 10 mandibular papillae) were examined in each patient, and the maximum score that each individual could reach was 100, allowing the value found in each individual to be expressed as a percentage. Subjects with GO scores ≥30 were classified as having clinically significant overgrowth as suggested previously.[10]

STATISTICAL ANALYSES

Individual patient data, including demographic, pharmacological and periodontal variables, were collected and transcribed into a statistical database.[‡] The comparison of variables among the groups was performed using the unpaired independent sample t, χ^2 statistic, or Mann-Whitney tests, as appropriate. Statistical data analysis accounted for sample size differences of the two groups. Data were initially examined using univariate regression analyzes to evaluate the effect of each independent variable on the prevalence and severity of GO, in both TcR and CsA groups. The effects of the variables on the GO scores were subsequently examined using both backward and forward stepwise regression analyzes and the general linear model. The regression coefficients, their 95% confidence interval (CI), and p-values were also reported.

RESULTS

The characteristics of the immunosuppressive groups, in relation to the presence and severity of GO, are shown in Table 1. Ten subjects were classified as presenting clinically significant GO (scores ≥30%). All of these subjects were in CsA group.

Table 1: The characteristics of the immunosuppressive groups, in relation to the presence and severity of GO

	CsA		*TcR*	
Clinically significant GO	*n*	*%*	*n*	*%*
Absence	50	83.3	40	100
Presence	10	16.7	0	0
Total	60	100	40	100

GO: Gingival overgrowth

[†]PCP-UNC 15, Hu-Friedy, Chicago, FL; [‡]Statistical Package for Social Sciences, Version 10.0 for Windows, SPSS, Chicago, IL

Table 2: Demographic, pharmacological and periodontal variables of subjects

	TcR				*CsA*				
	Mean	*SD*	*Min.*	*Max.*	*Mean*	*SD*	*Min.*	*Max.*	*p-value*
Age	31.85	8.85	18	47	39.08	9.90	20	68	<0.001
Weight (kg)	64.37	13.15	32	94	69.21	13.03	44	98	NS
Months of after RT	32.30	30.34	3	140	74.93	38.15	18	221	<0.001
Serum creatinine concentration (mg/dl)	1.33	0.38	0.70	2.30	1.39	0.49	0.60	2.90	NS
PI	0.98	0.63	0.22	2.35	1.33	0.77	0.10	3.00	<0.05
GI	0.47	0.38	0.10	1.43	1.87	0.68	0.11	3.00	<0.001
PPD	2.10	0.51	1.35	4.02	2.51	0.93	0.22	5.18	<0.05
PBI	0.36	0.31	0.00	1.50	0.62	0.63	0.00	3.00	<0.05
Daily dosage of TcR (mg/day)	4.55	2.37	1	13	—	—	—	—	—
Daily dosage of CsA (mg/day)	—	—	—	—	145.83	41.21	50	225	—
Daily dosage of glucocorticoid (mg/day)	5.82	1.87	4.00	10.00	5.69	1.79	4.00	15.00	NS
Blood TcR level (ng/ml)	7.69	2.96	4.3	22.9	—	—	—	—	—
Blood CsA level (ng/ml)	—	—	—	—	636.75	137	258	952	—
GO(%)	2.55	4.67	0.00	15	12.36	19.29	0.00	98.00	<0.01

SD: Standard deviation; NS: Not significant; RT: Renal transplantation; PI: Plaque index; GI: Gingival index; PPD: Probing pocket depth; PBI: Papilla bleeding index; GO: Gingival overgrowth

Table 3: The characteristics of individuals with and without GO in CsA group

	CsAGO(–)				*CsAGO(+)*				
	Mean	*SD*	*Min.*	*Max.*	*Mean*	*SD*	*Min.*	*Max.*	*p-value*
Age	38.74	10.47	20	68	40.80	6.40	31	54	NS
Weight (kg)	68.24	13.34	44	98	74.10	10.61	53	92	NS
Months of after RT	76.48	40.07	18	221	67.20	26.82	21	108	NS
Serum creatinine concentration (mg/dl)	1.40	0.48	0.80	2.90	1.37	0.59	0.60	2.50	NS
PI	1.11	0.61	0.10	3.00	2.41	0.54	1.66	3.00	<0.01
GI	0.70	0.47	0.11	2.22	1.75	0.93	0.27	3.00	<0.01
PPD	2.20	0.60	0.22	4.31	4.06	0.74	2.85	5.18	<0.01
PBI	0.45	0.40	0.00	1.90	1.49	0.84	0.70	3.00	<0.01
Daily dosage of glucocorticoid (mg/day)	5.85	1.93	5.00	15.00	4.90	0.31	4	5	<0.05
Daily dosage of CsA (mg/day)	141.50	42.13	50	200	167.50	28.98	150	225	NS
Blood CsA level (ng/ml)	636.76	124.5	258	895	636.70	196.6	384	952	NS
CsA mg/kg/gün	0.54	0.29	0.25	1.68	0.45	0.1	0.29	0.61	NS
GO(%)	5.08	7.01	0.00	24	48.80	20.04	31.00	98.00	<0.001

SD: Standard deviation; NS: Not significant; RT: Renal transplantation; PI: Plaque index; GI: Gingival index; PPD: Probing pocket depth; PBI: Papilla bleeding index; GO: Gingival overgrowth

Demographic, pharmacological and periodontal variables of subjects in the total sample, divided according to the presence/absence of GO, are detailed in Table 2. The length of time after transplantation was longer and statistically significant in CsA using group than TcR using group ($p < 0.001$). CsA group presented statistically significant all periodontal variables and higher PI ($p < 0.05$), higher GI ($p < 0.001$), higher PPD ($p < 0.05$), higher PBI ($p < 0.05$) and it was observed that the mean GOI was significantly higher in the CsA group than in the TcR group ($p < 0.01$).

A shown in Table 3, the characteristics of individuals with and without GO in CsA group. The number of patients in the CsA group with GO ($CsAGO^+$) was 10 and number of patients in the CsA group without GO ($CsAGO^-$) was 50.

When assessing the period throughout time, no significant alteration was observed and mean daily dosage of CsA higher in $CsAGO^+$ group but this difference is no significant. In addition, CsA blood levels were also similar in both groups. Daily dosage of glucocorticoid was significantly higher in $CsAGO^-$ group ($p < 0.05$). All periodontal values (PI, GI, PPD, PBI) were significantly higher in $CsAGO^+$ group ($p < 0.01$) and it was observed that the mean GOI was significantly higher also ($p < 0.001$).

DISCUSSION

A large portion of transplant subjects that take immunosuppressive drugs present significant functional, esthetic, and phonetic problems due to GO. Gingival overgrowth, for many reasons, depending on the immunosuppressant (CsA, TcR, etc.), calcium channel blockers (nifedipine) and

anticonvulsants (phenytoin) drugs occur as unwanted side effects.

When GO was evaluated within specific drug regimens, different authors reported higher prevalence rates for subjects medicated with CsA when compared with those medicated with TcR.[7,13,19,20] Indeed, prevalence rates of GO within CsA regimens have been reported to vary in the literature from 15 to 80%[13,20-22] and within TcR regimens from 0 to 30%.[7,13,14] Spolidorio et al[23] including those individuals with renal transplant who were using the 88 CsA and 67 Tac were not find gingival enlargement using TcR patients. Findings from the present study also demonstrated a higher occurrence of GO among subjects under CsA regimens when compared with TcR. When evaluating the occurrence of GO among subjects medicated with TcR, the present study showed a lower occurrence of GO when comparing with CsA. This occurrence was similar to other studies.[24,25]

Various studies[16,23-25] showed that the concomitant use of CsA and calcium channel blockers could produce a synergistic effect on GO in subjects taking these drugs. For this reason, we chose to exclude calcium channel blockers from the present study. To the best of our knowledge, a few studies have previously compared the GO in recipients with RT who used CsA or TcR in the absence of calcium channel blockers. First article[25] that evaluates and compares GO in recipients with RT who used CsA or TcR in the absence of calcium channel blockers showed that the GO mean was significantly lower in the TcR group than in the CsA group 180 days after transplantation. In this study, the TcR group showed a mean GO of 2.55% and the CsA group showed a mean of 12.36% after receiving RT ($p < 0.01$). In CsA group if the GO considered significant the percentage would be 16.7. Gingival overgrowth was not observed significantly in TcR group. The results of this study are similar to those obtained in the study by Paixão et al,[25] who observed a mean GO of 5.4% for the CsA group and 17.4% for the TcR group.

The GO cases caused by the use of drugs are observed in the anterior teeth in general, and in the labial surfaces in particular. As the overgrowth that initially holds the interdental area advances, this can expand on to the gingivial area and the margins of the gum.[21,26,27] For this reason, in order to identify GO more accurately, and in order to not ignore the aspect of 'GO that has clinical implications' that needs surgical intervention, we have observed and evaluated on the lower and higher anterior teeth of our case studies. There is a range of indexing systems available that considers observations about GO. In our study, we chose to adopt the methodological approach introduced by Seymour et al[18] to identify issues with GO, as this is the most acknowledged and commonly used clinical method. In addition, we refer to ≥ 30 as the 'GO that has clinical implications' in order to evaluate on the GO which needs surgery.[10,28]

There are two pieces of research which focus on identifying the effect of time after RT on the GO.[24,25] In our study, we have observed our patients once only and it was on the condition that it as at least 3 months after the RT. In the CsA group, the approximate time is 74.93 months and in the TcR, it is 32.30. By comparing the time, the RT statistical differences have been found to be ($p < 0.001$). The reason behind the increase in the GO within the CsA (compared to TcR) might be related to this statistical difference. However, the relationship between GO and the amount of time spent in using drugs do not signal a connection between the two.[7,13] In most cases, GO occurs between first and third month, and the longer time it takes, the slower GO occurs. In this regard, our study concurs with the results of other studies that prove that there are not any statistical links between $CsAGO^+$ and $CsAGO^-$.[29-31]

This study recorded the amount of immunosuppressants used by each individual on a daily basis. However, because the main immunosuppresants are different, we were not able to provide a comparative analysis between the patient groups who use Tac and CsA. Those patients in the group which used CsA, there was no difference between the $CsAGO^+$ and $CsAGO^-$ groups in terms of the daily dose of drugs. In considering the possible correlation between the patient's body weight, the dose used, and the GO we have compared the CsA doses per kilogram between the $CsAGO^+$ and $CsAGO^-$ groups; however, no differences were observed. Also, there were no differences as to blood levels between the two groups. This may be a result of the different numbers of patients in each group.

Previous research has demonstrated that azathioprine has anti-inflammatory qualities, and that in cases of immunosuppressive curing protocols, if used adjacent to CsA use, it requires a much lower CsA dose.[11,32] Seymour et al[33] compared two groups made up of 24 patients with renal transplants who use CsA and azatioprin, and found out that it does not have unwanted side effects on the periodontal tissues. In those patients who used azthioprine or prednizon, a lower level of CsA dose and CsA blood level has been identified. Wilson et al[34] and Thomason et al[32] identified a opposite correlation between azathioprine and prednizon doses and GO. Similarly, in our study, in the $CsAGO^+$ group, approximately daily levels of glucocorticoid was 4.90. In those in the $CsAGO^-$ the level was 5.85 (mg/day). This is meaningful statistically ($p < 0.05$).

An other study showed that plaque with CsA and stimulated salivary flow was reserve for the release of CsA.[35] Hallmon and Rossmann,[36] concluded that the

existence of plaque increases GO. Our research found a significant difference between CsA and TcR groups in regard to plaque index. In the TcR group, the approximate score for plaque index is 0.98 ± 0.63, and in the CsA group it is 1.33 ± 0.77. There are a number of studies in literature that concurs with our findings. It has been confirmed by studies that in the cases of GO that are caused by CsA the bacterial plaque formation is important and good dental hygiene may reduce GO and even be prevented this way.[10-12,31,37-39] Our findings demonstrate that there is a link between GO and plaque formation. While comparing $CsAGO^+$ and $CsAGO^-$ groups, it is established that the $CsAGO^+$ group has higher levels of plaque index ($p < 0.01$). It must be remembered that GO makes plaque retantion easier.

Gingival index values in the group that uses CsA are understandbly and statistically much higher than the group that used TcR ($p < 0.001$). In those patients who use CsA, the approximate GI rate is 1,87 ± 0,68; and in those who use TcR it is 0.47 ± 0.38. There are previous studies which concur with our finding.[30,31,40] However, stating that there are studies availiable showing no signi-ficant difference in GI.[33,41] In our study group of patient who are using CsA were examined, and found out that the gingival index scores in $CsAGO^+$ was significantly higher compare to $CsAGO^-$ ($p < 0.01$) according to these result, we can say that there is increase in value of GO and GI.

In our study, gingival enlargement was first observed in papillary regions of inflammation in the measure that we use to papillary bleeding index scores, in terms of CsA and TcR of the patient groups statistically significant difference was observed ($p < 0.05$). Papilla bleeding index average in CsA group was 0.62; but in TcR was recorded as 0.36. When we evaluate the CsA group, while the mean value in $CsAGO^-$ group is 0.45; $CsAGO^+$ is consider to be 1.49 and in which the difference between groups was statistically significant ($p < 0.01$). Similarly, Costa et al[13] revealed in their research that in both CsA and TcR using patients, there is a relationship between the power of GO and PBI. Our research argues that there is a positive link between GO and inflammation.

Increased pocket depth is found to be corrlated to GO when both CsA and TcR using group is compared to each other and CsA group. This is an expected result regarding GO and coronaly positioning of marginal gingiva and formation of pseudopocket.[41,42]

CONCLUSION

The results of our study show that GO does not occur in patients medicated with TcR, even if TcR shares the same mechanism with CsA. We think that TcR is a good choice for patients suffering from GO if a change about drug regimen is considered.

In order to evaluate and compare the long-term activity of TcR, we need to have a research that examines a much longer period of drug use.

CLINICAL RELEVANCE

- *Scientific rationale for the study*: Tacrolimus 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 cyclosporine A. Significant difference in the incidence of clinically significant GO was observed between groups.
- *Practical implications*: Tacrolimus seems to be a good alternative, with respect to the oral condition, for transplant recipients who require immunosuppressive therapy. Dentistry is varying with induction of modern science to practice dentistry.[43]

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