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Prevalence of gingival overgrowth in transplant patients immunosuppressed with tacrolimus

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Abstract

Aims: The study aims to determine the prevalence and severity of gingival overgrowth in a group of adult organ transplant recipients immunosuppressed with tacrolimus in comparison with ciclosporin, and to examine various risk factors for the development of gingival overgrowth.

Methods: Forty patients taking tacrolimus were compared with 197 ciclosporin patients. Demographic, pharmacological and periodontal data were recorded for all patients. Comparison between the groups was made using independent sample *t*-tests, χ^2 statistic or Mann–Whitney test. The effects of risk variables on overgrowth severity were examined using forward and backward stepwise regression analysis.

Results: Those taking tacrolimus had a significantly lower mean gingival overgrowth score (14.1%) compared with ciclosporin (22.4%). Fifteen percent of the tacrolimus group had clinically significant gingival overgrowth compared with 30% in the ciclosporin group ($p = 0.053$).

Conclusions: The prevalence and severity of gingival overgrowth is less in adult transplant patients taking tacrolimus compared with ciclosporin. Concomitant use of calcium channel blockers and previous medication with ciclosporin are significant risk factors for the presence and severity of gingival overgrowth. Patients who have alteration of their immunosuppressant from ciclosporin to tacrolimus may persist in demonstrating gingival overgrowth attributable to their ongoing therapy with calcium channel blockers.

Key words: gingival overgrowth; tacrolimus; transplant

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Tacrolimus (formerly known as FK506) was introduced as an immunosuppressive agent for use in organ transplants in 1987 and has gradually been gaining popularity. The pharmacodynamics of tacrolimus are very similar to ciclosporin (Spencer et al. 1997). Tacrolimus binds with FK binding proteins to form a complex, in a similar way to which ciclosporin binds to ciclophilins. The resultant complexes inhibit calcineurin activity, thus inhibiting calcium-dependent events (Fruman et al. 1992). This leads to reduced IL-2 gene transcription, nitric oxide synthetase activation, and cell degranulation and apoptosis (Wiederrecht 1993). Glucocorticoid and progesterone action is potentiated and the TGF-β1 gene may be enhanced. As with ciclosporin, Type 1 T-helper cells are suppressed preferentially to Type 2 helper cells, and T-cell-mediated toxicity is impaired (Thomson et al. 1995). Tacrolimus has an immunosuppressive capacity 100 times that of ciclosporin (Jacobson et al. 1998), and is recognised as an effective alternative to ciclosporin in primary and rescue therapy. In primary therapy it has been suggested that it may be more effective than ciclosporin in preventing acute and chronic rejection of liver transplants (Spencer et al. 1997). Tacrolimus shares many unwanted effects common to other immunosuppressive agents. It demonstrates an increased tendency for patients to develop diabetes and neurotoxicity as compared with ciclosporin (Mueller et al. 1994, Marchetti & Navalesi 2000), and similar levels of nephrotoxicity (Porayko et al. 1994). By contrast, hyperlipidaemia, hypertension

and hirsutism are less likely with tacrolimus than ciclosporin (Mihatsch et al. 1998).

A number of case reports suggest that the severity of gingival overgrowth seen in patients taking tacrolimus is less than that with ciclosporin. The first such report detailed a 59-year-old male hepatic transplant recipient changed from ciclosporin to tacrolimus 3 years post-transplant. After 2 months on the new drug regime, the extent of gingival overgrowth was reported to have decreased by 50% to an 'acceptable level' (Bader et al. 1998). Further case reports support this observation of reduction, and in some cases complete resolution, of gingival overgrowth when subjects have been changed from ciclosporin to tacrolimus (Hernandez et al. 2000, Thorp et al. 2000, Kennedy & Linden 2000, James et al. 2000).

Prevalence studies are limited and the methods used for assessing overgrowth and severity vary from study to study (Sheehy et al. 1996, Williams et al. 1996, James et al. 2001, Oettinger-Barak et al. 2001, Wondimu et al. 2001). Few authors define a cut-off point at which overgrowth is said to be present, nor do they define a level at which they regard the overgrowth to be clinically significant. Nevertheless, the consensus of the research thus far would suggest that tacrolimus causes less overgrowth than ciclosporin, and that when overgrowth does occur it is less severe. To date there has been no research examining the role of calcium channel blockers in gingival overgrowth induced by tacrolimus.

A high proportion of organ transplant recipients are concomitantly medicated with calcium channel blockers, usually nifedipine, for a number of reasons. Nifedipine ameliorates the nephrotoxicity of ciclosporin (Feehally et al. 1987) and may have a similar beneficial effect with tacrolimus. In hepatic transplant recipients, concomitant medication with nifedipine has also been shown to reduce the dose of tacrolimus needed to prevent rejection (Seifeldin et al. 1997).

Concomitant medication with nifedipine has been shown to increase both the prevalence and severity of gingival overgrowth in patients taking ciclosporin (Slavin & Taylor 1987, Pan et al. 1992, Pernu et al. 1993, Thomason et al. 1993, 1995), and one paper has commented that the overgrowth in patients taking tacrolimus appears to be more severe when calcium channel blockers are also taken (James et al. 2001).

Aim

The aims of this investigation were to determine the prevalence and severity of gingival overgrowth in a group of adult organ transplant recipients immunosuppressed with tacrolimus or ciclosporin, and to examine the role of a range of demographic, pharmacological and periodontal risk variables on gingival overgrowth in patients medicated with tacrolimus

Materials and Methods

The present study received ethical approval from the appropriate Hospital and University Joint Ethical Committee. Informed written consent was obtained from each patient. All transplant subjects were recruited from the organ transplant clinics at the Freeman Hospital, Newcastle upon Tyne where they are seen on a regular basis to monitor drug therapy and graft survival. All subjects were at least 1-month post-transplant and medicated with either ciclosporin or tacrolimus together with a range of other drugs. Only patients who possessed a minimum of six of the eight most anterior teeth in the upper or lower dental arches participated in the study. Demographic variables including age, gender and time since transplant were recorded for each patient.

One clinician (J. S. E.) undertook a gingival examination of all subjects. The six most anterior teeth in each arch were assessed for plaque using the system described by Silness & Loe (1964), and the papillary bleeding index was recorded (Saxer & Muhlemann 1975).

Upper and lower alginate impressions of each subject were taken, from which plaster models were prepared. Gingival overgrowth was scored on the models as described previously (Seymour et al. 1985). The gingival overgrowth score was determined by a second clinician (J. M. T.) who was blinded to the subjects' identity and medical history. Patients with overgrowth scores of $\geqslant 30$ were classified as having clinically significant overgrowth as previously outlined (Thomason et al. 1992, 1993).

Pharmacological variables

A full drug history was obtained from each patient, including any previous medication with ciclosporin. Patients are screened regularly for whole blood and serum trough concentrations of ciclosporin, or tacrolimus. Creatinine serum levels are measured as a monitor of renal function and were available as part of the patients' routine examination on the transplant clinics. Data from the most recent assessments, usually on the day of examination, were recorded and used in the analysis.

Statistical analysis

Individual patient data, including demographic, pharmacological and periodontal variables, were collected and transcribed onto a statistical database (Minitab 2000). Data were examined for the presence of obvious outliers caused by typing or transcription errors and these were corrected. The comparison of the variables listed in Table 1, between the two groups, was made using independent sample *t*-tests, the χ^2 statistic or the Mann–Whitney test as appropriate. The continuous data sets were examined for normality using simple histogram plots.

Data relating to those subjects taking tacrolimus were examined initially using univariate regression analysis to evaluate the effect of each of the independent variables on the severity of gingival overgrowth. The effects of the variables listed in Table 3 on the gingival overgrowth score were subsequently examined using both backward and forward stepwise regression analysis and the general linear model (Stata 1993). The regression coefficients, their 95% confidence intervals (CIs) and *p*-values are reported.

Results

Forty subjects medicated with tacrolimus participated in the study. Their demographic, pharmacological and periodontal data were compared with a group of 197 subjects medicated with ciclosporin (Table 1). The tacrolimus group was younger (41.3 years) than the ciclosporin group (47.8 years) ($p = 0.009$).

Overall, only 25 patients (11%) were not medicated with prednisolone: 23 in the ciclosporin group and two in the tacrolimus group. The median dosage of prednisolone in the ciclosporin group (6 mg/day) was lower ($p = 0.019$) than for patients medicated with tacrolimus (8.75 mg/day). Fewer patients ($n = 165$, 70%) were medicated with azathioprine: 138 in the ciclosporin group and 27 in patients medicated with tacrolimus. The differences between these groups were not significant (Table 1).

The ciclosporin group had more severe gingival overgrowth scores (22.4 ± 17.1) than in the tacrolimus group (14.1 ± 12.5): a difference of 8 units (95% CI 3.7, 12.7, $p = 0.0006$). Of the patients medicated with ciclosporin, 59 (30%) had clinically significant overgrowth compared with 15% (six patients) in the tacrolimus group, but these differences were only marginally significant ($p = 0.053$).

The demographic, pharmacological and periodontal data for the tacrolimus subjects, dichotomised into those taking calcium channel blockers or not, are reported in Table 2. The two groups had similar profiles. Gingival overgrowth scores in the tacrolimus group were greater when they were concomitantly medicated with calcium channel blockers (21.3%) compared with those taking no calcium channel blockers (8.18%, $p = 0.001$).

Univariate regression modelling of gingival overgrowth severity in the tacrolimus group identified a number of independent variables as risk factors for overgrowth severity: age, azathioprine dosage, medication with a calcium channel blocker, plaque index, papilla bleeding index and previous medication with ciclosporin (Table 3). No relationship between the severity of overgrowth and either the tacrolimus dosage or blood levels was identified.

Stepwise regression modelling and the general linear model were used to identify risk factors for the severity of overgrowth in this group of patients and the result of the final model is shown as Table 4. The addition of other variables failed to improve this final model ($p < 0.0001$, adjusted $R^2 = 0.55$).

Table 1. Demographic, drug and periodontal variables of transplant patients grouped according to main immunosuppressive agent

	tacrolimus ($n = 40$)	ciclosporin ($n = 197$)	p-value
% male (number)	60 (24)	75 (147)	0.060
age (years) – mean ± SD (range)	41.3 ± 13.6 (18–62)	47.7 ± 13.6 (18–78)	0.009
time since transplant (range in months)	31.0 (2–115)	42 (1–264)	0.271
daily dosage of prednisolone (mg) (range)	8.75 (0–60)	6.0 (0–85)	0.019
mean daily dosage of azathioprine (mg) (range)	50 (0–150)	50 (0–500)	0.828
% of subjects taking calcium channel blockers (number)	45 (18)	49 (97)	0.625
plaque score (range)	0.57 (0–1.65)	0.50 (0–2.19)	0.167
papillary bleeding index (range)	0.19 (0–1.45)	0.34 (1–3.0)	0.147
mean gingival overgrowth score % (SD)	14.1 (±2.5)	22.4 (±17.1)	0.003
% with clinically significant overgrowth (number)	15 (6)	30 (59)	0.053

Median and range unless stated.

Table 2. Demographic, drug and periodontal variables of transplant patients immunosuppressed with tacrolimus and dichotomised according to concomitant calcium channel blocker

	tacrolimus alone ($n = 22$)	tacrolimus+calcium channel blocker ($n = 18$)	p-value
age (years) – mean	44.0	38.0	0.17
weight (kg) – mean	69.4	72.2	0.60
months since transplant	31.0	29.5	0.66
daily azathioprine dose (mg)	62.5	50.0	0.96
daily prednisolone dose (mg)	7.5	10.0	0.52
creatinine	163.0	168.5	0.161
serum conc. tacrolimus	11.3	9.0	0.148
tacrolimus dose (mg)	6.5	6.0	0.68
papillary bleeding index	0.166	0.214	0.29
plaque index	0.468	0.690	0.463
mean gingival overgrowth score (%)	8.18	21.3	0.001

Median unless stated.

Table 3. Results of univariate analysis of those subjects taking tacrolimus

	regression coefficient	SE for slope	p-value for slope	95% CI for slope		adjusted R^2%
gender	− 5.65	3.97	0.163	− 13.68	2.39	2.56
age	− 0.32	0.14	0.026	− 0.60	− 0.04	10.02
duration of transplant	− 0.04	0.07	0.548	− 0.18	0.10	1.65
weight	− 0.22	0.12	0.089	− 0.47	0.03	4.98
azathioprine dosage	− 0.09	0.04	0.013	− 0.18	− 0.02	12.85
prednisolone dosage	0.27	0.17	0.131	− 0.08	0.62	3.43
calcium channel blocker	13.09	3.40	0.000	6.21	19.99	26.15
plasma creatinine conc.	0.00	0.25	0.846	− 0.05	0.05	− 2.53
serum tacrolimus conc.	− 0.46	0.55	0.413	− 1.57	0.66	0.86
tacrolimus dose	0.98	0.68	0.162	− 0.41	2.37	2.57
previous ciclosporin	7.44	3.83	0.059	− 0.31	15.18	6.66
papillary bleeding index	14.59	5.26	0.008	3.96	25.22	14.70
plaque index	8.44	3.92	0.038	0.49	16.39	8.49

Discussion

Gingival overgrowth is a significant problem in transplant patients, and yet one that to date has not been possible to avoid in the susceptible subject. Patients require immunosuppression for life, and until the introduction of tacrolimus there had been little alternative to ciclosporin. Clinical experience with tacrolimus and the little published data suggests that tacrolimus does not induce gingival overgrowth, or if it does, the severity is less than with ciclosporin. Nevertheless, overgrowth has been reported in patients medicated with tacrolimus (Williams et al. 1996), and this may be more severe in patients also medicated with calcium channel blockers (James et al. 2001). These results are based on the largest reported group of transplant patients medicated with tacrolimus, compared with patients medicated with ciclosporin. The finding that the tacrolimus group had a higher prednisolone dose is surprising as it has been previously suggested that one of the advantages of tacrolimus over

Table 4. Forward stepwise regression analysis investigating the relationship between gingival overgrowth score and the variables of age, gender (male = 1, female = 2), duration of transplant, weight, prednisolone dosage, azathioprine dosage, plasma creatinine conc., tacrolimus dosage, plaque scores, papillary bleeding index, and medicated with calcium channel blocker (yes = 1, no = 2) ($n = 40$)

	regression coefficient	*p*-value	95% confidence interval for regression coefficient	
calcium channel blocker	13.39	<0.0001	7.94	18.84
azathioprine dose	-0.06	0.049	-0.12	-0.000
periodontal bleeding index	10.24	0.017	1.96	18.51
previous ciclosporin	8.07	0.005	2.59	13.56
constant	5.72	0.071	-0.51	11.94

Age, gender (male = 1, female = 2), duration of transplant, weight, prednisolone dosage, plasma creatinine conc., tacrolimus dosage and plaque scores not included in the final model.
Adjusted R^2 for the model = 55% ($p<0.0001$).

ciclosporin is the ability to reduce prednisolone dosage (Spencer et al. 1997).

Gingival overgrowth was seen in both groups but the severity of the changes was greater in the ciclosporin comparator group, and the difference in the prevalence of clinically significant overgrowth between the two groups was only marginally significant ($p = 0.053$). These findings support those of previous studies. Nevertheless, six subjects (15%) medicated with tacrolimus in the present study had clinically significant gingival changes that warrant surgical intervention. The prevalence of gingival overgrowth induced by calcium channel blockers alone (nifedipine 6%, amlodipine 1.7%) (Ellis et al. 1999) suggests that the occurrence of gingival overgrowth in this group cannot be explained solely by the concomitant calcium channel blocker. The interrelationship between plaque, gingival inflammation and gingival overgrowth has been explored previously (Seymour et al. 1996, 2000) and the role of inflammation as a risk factor for gingival overgrowth has been reported (Thomason 1995, Thomason et al. 1996). However, oral hygiene levels of the two groups were similar, and while the severity of gingival inflammation was greater in the ciclosporin group, the differences were not statistically significant and therefore offers little further insight.

A protective effect of azathioprine in transplant patients has been suggested by some authors. Azathioprine may exert its effect via the reduction in ciclosporin dosage that azathioprine allows (Wilson et al. 1998). This supports an earlier report which suggested that patients medicated with azathioprine had lower gingival overgrowth scores than those not taking azathioprine, and that this too was related to lower ciclosporin blood concentrations in the azathioprine group (Somacarrera et al. 1994). It has been suggested more recently that azathioprine may exert a protective effect directly through its anti-inflammatory properties (Thomason et al. unpublished results).

Univariate analysis indicates that in addition to concomitant medication with a calcium channel blocker, overgrowth was more severe in younger patients, those with poor oral hygiene and gingival inflammation and in patients with low azathioprine dosage regimens. The inverse relationship between age and the severity of gingival changes has been a regular finding (Thomason et al. 1992, 1993). Plaque score was dropped from the final multivariate model as the addition of plaque score did not contribute further information on the variability of gingival overgrowth score (Table 4). The degree of correlation between the independent variables themselves impacts on the selection of predictor variables for the final model and correlated pairs are not usually both included (Altman 1991). The loss of plaque score in favour of papillary bleeding index in these models is in line with our earlier studies in patients medicated with ciclosporin (Thomason et al. 1995).

It can be seen that concomitant medication with a calcium channel blocker does present an increased risk of developing severe gingival changes in patients medicated with tacrolimus. Patients medicated with calcium channel blockers are at risk of approximately 13 additional gingival overgrowth units than those not medicated with the drug. Calcium channel blocker medication alone, only accounts for 26% of the variation in overgrowth score ($R^2 = 0.262$) in patients medicated with tacrolimus. The first model, not including previous medication with ciclosporin, accounts for 45% of the overgrowth variation ($R^2 = 0.453$) (not shown). Including previous medication with ciclosporin results in a final model that describes 10% more of the variation in overgrowth scores (adjusted $R^2 = 0.550$), suggesting that, in this group of patients at least, some of the gingival overgrowth observed may result from earlier ciclosporin therapy (Table 4).

Examination of the drug history of the six tacrolimus patients with significant gingival overgrowth revealed that four of these cases did indeed have a history of previous medication with ciclosporin; however, we have no measure of their gingival condition prior to dosing with tacrolimus.

The findings from this study demonstrate that drug-induced gingival overgrowth is a significant problem in transplant patients medicated with tacrolimus, although the severity is less than that seen in patients medicated with ciclosporin. The major risk factor would appear to be medication with a calcium channel blocker. Other significant predisposing factors for the severity of gingival overgrowth in transplant patients medicated with tacrolimus are the papillary bleeding index, dosage of azathioprine and previous medication with ciclosporin. As always in a cross-sectional study of this type, it is not possible to determine if the relationship between gingival overgrowth and papillary bleeding index is causal or incidental, and it should be remembered that an improved oral hygiene regimen has failed to prevent the occurrence of ciclosporin-induced gingival overgrowth in renal transplant patients (Seymour & Smith 1991).

Earlier studies have suggested that alteration of drug therapy from ciclosporin to tacrolimus may bring about resolution of gingival overgrowth. As a result of this work, the authors suggest that this is not always the case, and in some cases overgrowth due to ciclosporin may persist after alteration to tacrolimus.

In our sample of 40 patients, two were seen to have overgrowth of a significant nature that could be solely attributable to tacrolimus and/or calcium channel blocker. If we are to extrapolate this figure crudely, one might suggest a prevalence of gingival overgrowth of

5%, which is not dissimilar to that for nifedipine alone (Ellis et al. 1999).

The challenge of future research is to gather information from transplant recipients who have only ever been immunosuppressed with tacrolimus in order to assess whether the changes described in this paper are attributable to the calcium channel blocker alone or a synergistic effect of the drug combination.

In conclusion, our results have shown that the prevalence and severity of gingival overgrowth is less in adult transplant patients taking tacrolimus compared with those taking ciclosporin. Also, the major risk factor for overgrowth in patients medicated with tacrolimus is concomitant calcium channel blocker. In those cases presenting with clinically significant overgrowth, the overgrowth is largely attributable to the calcium channel blocker but this effect may be enhanced by previous exposure to ciclosporin or to the presence of tacrolimus.

Patients who have had alteration of their immunosuppressant from ciclosporin to tacrolimus may persist in demonstrating gingival overgrowth, which may be attributable to their ongoing calcium channel blocker therapy. Thus, the presence of severe overgrowth with ciclosporin may not in itself be justification for altering a patient's immunosuppressant regimen.

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