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Risk factors for gingival overgrowth in patients medicated with ciclosporin in the absence of calcium channel blockers

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Abstract

Objectives: This study investigates the effect of a range of potential risk factors on the severity of gingival overgrowth in transplant patients medicated with ciclosporin in the absence of any calcium channel blockers.

Materials and Methods: One hundred dentate solid organ transplants medicated with ciclosporin (but not calcium channel blockers or phenytoin) were recruited for the study. Demographic, pharmacological and periodontal data were recorded and gingival overgrowth assessed from stone models.

Results: Univariate analysis identified the duration of transplant, papilla bleeding index, creatinine serum concentration, azathioprine and prednisolone dosage as risk factors for overgrowth severity. Multivariate modelling, excluding the periodontal parameters, gave a predictive model that included dosages of ciclosporin, azathioprine, prednisolone and weight ($p < 0.0001$, adjusted-$R^2 = 19\%$). Adding the periodontal variables strengthened the model ($p < 0.0001$, adjusted-$R^2 = 34.5\%$).

Conclusion: The explanatory models in this study contain a number of variables that moderate inflammation (azathioprine and prednisolone) or are markers of it (papilla bleeding index). Dosage of each of the three immunosuppressants was identified as a risk factor for the severity of gingival change. This observation appears to have been masked by the effects of the calcium channel blockers in earlier studies.

Key words: azathioprine; ciclosporin; gingival overgrowth; inflammation; prednisolone; transplant

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Ciclosporin remains the immunosuppressant of choice for most solid organ transplant patients and is usually used in combination with other immunosuppressants such as azathioprine and prednisolone (Dunn et al. 2001). These three principle agents may produce a host of unwanted effects such as renal and hepatic impairment, bone marrow suppression, diabetes and osteoporosis (Faulds et al. 1993). Of particular concern for the dental profession is the management of ciclosporin-induced gingival overgrowth, first reported in the dental literature in 1983 (Rateitschak-Plüss et al. 1983). The role of ciclosporin in this condition is now well documented. Approximately 25–30% of patients medicated with ciclosporin experience this unwanted effect at a level severe enough to warrant surgical reduction of the gingival tissues (Thomason et al. 1995). An increased prevalence of the condition occurs in patients concomitantly medicated with nifedipine (Slavin & Taylor 1987). Indeed the number of patients with clinically significant overgrowth may more than double in patients who are also medicated with a calcium channel blocking drug (Thomason et al. 1996). The effect of calcium channel blockers on the severity of gingival overgrowth is now largely accepted (Seymour et al. 1996) and appears to be related to the plasma concentration of the drug (Thomason et al. 1997). A range of other risk factors for ciclosporin-induced gingival overgrowth has been identified (Thomason et al. 1995, 1996) including age, sex, duration of therapy, gingival inflammation and creatinine serum concentration.

It has also been postulated that some form of threshold dosage of ciclosporin is required to induce the changes (Daley et al. 1986), although most authors have reported no correlation with ciclosporin

blood levels (McGaw et al. 1987; Pan et al. 1992; Pernu et al. 1992a; King et al. 1993; O'Valle et al. 1994; Thomason et al. 1995). Nevertheless, recent evidence has suggested that the patient's last measured ciclosporin blood concentration may be an important determinant of this condition (Thomas et al. 2001).

There is a wealth of literature relating directly to the role of ciclosporin in this unwanted effect but relatively little is known of the function of other immunosuppressive agents in gingival overgrowth. An inverse relationship between gingival overgrowth and azathioprine and prednisolone dosage has been reported in adults (Somacarrera et al. 1994a, Wilson et al. 1998). Contrary findings have also been reported in cardiac transplant patients medicated with prednisolone, azathioprine and ciclosporin although some caveats were expressed (Thomason 1995). From the published data available, the role of these drugs in ciclosporin-induced gingival overgrowth is unclear, as is the nature of the risk they may pose. Part of the reason for the paucity of data on the effect of the other immunosuppressants and the uncertainty regarding the effect of ciclosporin pharmacokinetics may relate to the difficulty of untangling the effect of these two drugs on gingival overgrowth from the synergistic effects of the calcium channel blockers.

The purpose of this study was to investigate the effect of a range of potential risk factors on the severity of gingival overgrowth in transplant patients medicated with ciclosporin in the absence of any calcium channel blockers.

Materials and Method

One hundred dentate subjects who had received solid organ transplants participated in the study, which had received prior ethical approval from the Joint Health Authority/University Ethics Committee. Informed written consent was obtained from each patient. All patients were recruited from the Cardio-Thoracic or Renal Units, of the Freeman Hospital, Newcastle upon Tyne, where patients are reviewed on a regular basis, and the viability and function of their transplanted organs monitored. All patients were more than 1 month post-transplant and medicated with ciclosporin. Patients concomitantly medicated with a calcium channel blocking drug or phenytoin were excluded from the study. Assessment of periodontal parameters was made on the papilla associated with the six most anterior teeth in each arch as in previous studies. This reflects both the pattern of tooth loss and the predilection for the anterior gingiva (Somacarrera et al. 1994b; Thomason et al. 1996). Probing depths, attachment loss and radiographs were not undertaken, and deemed to be inappropriate given that the primary outcome variable was gingival overgrowth. Oral hygiene, gingival inflammation and the prevalence and severity of gingival overgrowth were examined by one investigator (JSE).

Oral hygiene

The level of oral hygiene was assessed using the plaque index system of Silness & Loe (1964). Measurements were made on the lingual, labial and interproximal surfaces. Scores for each site were summed and the mean values assigned.

Gingival inflammation

The patient's gingival condition was assessed using the papilla bleeding index of Saxer & Muhlemann (1975). This was performed by provoking the gingiva by sweeping the sulcus from the base of the papilla to its tip along the tooth's mesial and distal aspects on both buccal and lingual aspects with a blunt periodontal probe under light finger pressure. After 30 s, the intensity of any resultant bleeding was scored (no bleeding scoring 0, spot bleeding scoring 1, fine line or several spots scoring 2, interdental papilla filling with blood scoring 3, and profuse bleeding 4). As with the gingival overgrowth index, the assessment site is centred on the interdental papillae.

Gingival overgrowth

Upper and lower full-mouth alginate impressions were taken for each patient. Gingival overgrowth was assessed on the plaster study models by one of the authors (JMT) without prior knowledge of the patient's details. Models were scored using the system described by Seymour et al. (1985). The buccal and lingual/palatal papilla associated with the six most anterior upper and lower teeth is each ascribed a score of between 0 and 5 depending on the amount of both horizontal and vertical enlargement. A total of 20 such papilla are thus selected and examined giving a potential maximum overgrowth score of 100 which can be expressed as a percentage. Patients with overgrowth scores of $\geqslant 30$ were assigned as having clinically significant overgrowth as outlined in previous studies. This score most appropriately coincides with a severity of overgrowth that warrants surgical intervention (Thomason et al. 1992, 1993).

Pharmacological variables

A full drug history was documented for each subject. As part of long-term management, transplant patients are screened regularly for creatinine serum concentration to assess renal function and whole blood concentrations of ciclosporin. The whole blood concentrations of ciclosporin and creatinine serum concentration were measured on the day of the periodontal screening, recorded and used in the analysis.

Statistical analysis

The comparison of variables listed in Table 1, between the two groups (i.e. those patients with clinically significant overgrowth and those with little or no changes), was made using the unpaired *t*-test, the χ^2 statistic and the Mann–Whitney test as appropriate. Using the dichotomous variable, clinically significant overgrowth, as the dependent variable, the data were investigated using univariate and multivariate logistic modelling techniques.

The effect of a range of independent variables on the severity of the gingival changes was assessed using both univariate and multivariate regression analysis. Data for the univariate analysis are presented in Table 2 in the form of regression equations. The standard error, *p*-values and 95% confidence intervals for the slopes are shown and the R^2 values for equations significant at the 5% level are given. The effect of combinations of these independent variables on the dependent variable, gingival overgrowth score, was further analysed using forward and backward stepwise regression analysis and the general linear model. Final models are presented in Tables 3 and 4 with regression coefficients, *p*-values and 95% confidence intervals for variables retained in the models.

Table 1. Demographic details and periodontal variables in transplant patients categorized by the presence of clinically significant overgrowth.

	Overgrowth $<30\%$	Clinically significant overgrowth, overgrowth $\geqslant 30\%$
Number of patients	84	16
Gender distribution (M:F)	54:30	12:4
Age (years)	45.6 ± 13.9	45.6 ± 15.2
Duration of transplant (months) median and range	31 (1–213)	33.5 (11–121)
Plaque score median and range	0.43 (0–2.19)	0.77* (0.1–1.89)
Papillary bleeding index median and range	0 (0–1.66)	0.166† (0–1.67)
Weight (kg)	70.7 ± 14.7	78 ± 18.2
Ciclosporin dosage (mg/day)	324 ± 172	311 ± 106
Creatinine serum concentration	139.8 ± 29.5	127.5 ± 18.8‡
Whole blood concentration of ciclosporin (μg/l)	220 ± 144	192 ± 68.6
Prednisolone dosage (mg/day) median and range	7 (0–25)	6 (0–9)
Azathioprine dosage (mg/day) median and range	50 (0–225)	25 (0–125)

Significant difference between groups;
*$p = 0.036$;
†$p = 0.001$;
‡$p = 0.038$.
Data shown as mean ± standard deviation unless stated.

Table 2. Severity of gingival overgrowth in transplant patients

Regression equation	SE for slope	p-Value for slope	95% CI for slope
$20.44 - 0.07 \times$ age (years)	0.09	0.44	− 0.24, 0.10
$20.90 - 2.60 \times$ gender (M = 1, F = 2)	2.53	0.31	− 7.62, 2.42
$13.77 + 0.09 \times$ duration (months)*	0.03	0.003	0.03, 0.15
$9.38 + 0.11 \times$ weight (kg)	0.08	0.15	− 0.04, 0.27
$20.00 - 0.01 \times$ ciclosporin dose	0.01	0.28	− 0.02, 0.01
$21.99 - 0.02 \times$ ciclosporin blood level†	0.01	0.017	− 0.04, − 0.004
$23.21 - 0.05 \times$ azathioprine dose‡	0.02	0.002	− 0.08, − 0.02
$21.00 - 0.43 \times$ prednisolone dose§	0.12	0.001	− 0.67, − 0.19
$29.10 - 0.08 \times$ creatinine serum conc¶	0.04	0.046	− 0.17, 0.002
$13.93 + 14.46 \times$ papilla bleeding index ‖	2.60	<0.0001	9.30, 19.61
$15.07 + 3.87 \times$ plaque score	2.25	0.087	− 0.57, 8.35

R^2 values for equations with p-values $\leqslant 0.05$:
*$R^2 = 7\%$;
†$R^2 = 4.7\%$;
‡$R^2 = 8\%$;
§$R^2 = 10.7\%$;
¶$R^2 = 3\%$;
‖ $R^2 = 23.2\%$.
Univariate regression analysis-outcome variable is % gingival overgrowth ($n = 100$).
The regression equation is in the form % gingival overgrowth = constant ± regression coefficient × variable.

Table 3. Backward stepwise regression analysis investigating relationship between percentage gingival overgrowth score and the variables of age, gender (male = 1, female = 2), duration of transplant, weight, ciclosporin dosage, ciclosporin whole blood concentration, prednisolone dosage, azathioprine dosage, creatinine plasma level ($n = 100$)

	Regression coefficient	p-Value	95% confidence interval for regression coefficient	
Ciclosporin dose	0.017	0.042	0.0007	0.034
Prednisolone dose	− 0.46	0.002	− 0.74	− 0.17
Azathioprine dose	− 0.054	0.010	− 0.096	− 0.013
Weight	0.19	0.009	0.05	0.34
Constant	4.78	0.421	− 6.96	16.52

Age, gender (male = 1, female = 2), duration of transplant, ciclosporin whole blood concentration, creatinine plasma level dropped from the final model adjusted-$R^2 = 19\%$.

Results

Data were collected for the 100 subjects participating in the study. The demographic, periodontal and pharmacological details are listed in Table 1. Ciclosporin variables for patients grouped by medication with azathioprine and prednisolone are shown in Table 5. Sixty-one of the subjects were recipients of heart transplants, 28 of lung transplants and the remaining 11 of renal transplants. All subjects were more than 1 month post-transplant with 82 subjects being more than 6 months post-transplant. The subjects were initially dichotomized into those with little or no gingival changes (scores $<30\%$) and those with clinically significant overgrowth (scores $\geqslant 30\%$). Sixteen per cent of patients in the study had clinically significant overgrowth. The mean age of the patients in each group was 45.6 years and the male:female ratios were not significantly different between groups ($p > 0.05$). Patients with clinically significant gingival overgrowth had higher plaque scores ($p = 0.036$), papilla bleeding index ($p = 0.001$) and lower creatinine serum concentration ($p = 0.038$), than those with little or no gingival changes, but the dosages of ciclosporin, prednisolone and azathioprine and the whole blood concentrations of ciclosporin were not significantly different between groups.

Univariate regression analysis highlighted significant relationships between clinically significant overgrowth and papillary bleeding index (odds ratio = 6.61, $p = 0.001$) and a marginally significant relationship with prednisolone dosage (odds ratio = 0.88, $p = 0.052$). Multivariate modelling produced no changes in the final model, and no other variable was identified as a significant risk factor for clinically significant overgrowth at the 5% level once adjusted for the effect of papilla bleeding index.

A number of variables were identified as potential risk factors for the severity of the gingival changes (Table 2). Duration since transplant (coefficient (coef) = 0.09, $p = 0.003$) and the papilla bleeding index (coef = 14.46, $p < 0.0001$) were identified as positive risk factors while creatinine serum concentration (coef − 0.08), $p = 0.046$), together with azathioprine dosage (coef = − 0.05, $p = 0.002$) and prednisolone dosage (coef = − 0.43, $p = 0.001$), appeared to offer some protection. Modelling gingival overgrowth severity as the dependent

Table 4. Backward stepwise regression analysis investigating the relationship between % gingival overgrowth score and the variables of age, gender (male = 1, female = 2), duration of transplant, weight, ciclosporin dosage, ciclosporin whole blood concentration, prednisolone dosage, azathioprine dosage, creatinine plasma level, plaque score, papilla bleeding index

($n = 100$)	Regression coefficient	p-Value	95% confidence interval for regression coefficient	
Ciclosporin dose	0.015	0.043	0.0005	0.030
Papilla bleeding index	13.41	<0.0001	8.60	18.22
Duration of transplant	0.07	0.012	0.016	0.13
Prednisolone dose	-0.38	0.003	-0.63	-0.13
Constant	9.39	0.004	3.15	15.6

Age, gender (male = 1, female = 2), weight, ciclosporin whole blood concentration, azathioprine dosage, creatinine plasma level, plaque score dropped from the final model. Adjusted-$R^2 = 34.5\%$.

Table 5. Ciclosporin variables in patients medicated with and without azathioprine and prednisolone

	Medicated with Azathioprine	Not medicated with Azathioprine	p-Value	95% CI
Ciclosporin dosage (mg/day)	263 ± 101	354 ± 180	0.0015	$-148, -36$
Whole blood concentration of ciclosporin (μg/l)	173.5 ± 80.1	238 ± 153	0.0064	$-111, -19$
	Medicated with prednisolone	Not medicated with prednisolone	p-Value	95% CI
Ciclosporin dosage (mg/day)	243.2 ± 74.0	329 ± 162	0.0024	$-140, -32$
Whole blood concentration of ciclosporin (μg/l)	148.1 ± 67.3	222 ± 135	0.003	$-121, -27$

variable with independent variables, excluding the periodontal parameters, gave a final predictive model shown in Table 3 ($p < 0.0001$, adjusted-$R^2 = 19\%$). The effect of adding the periodontal variables to the modelling process is shown in Table 4. This model describes a greater proportion of the variation in the overgrowth score than the previous model ($p < 0.0001$, adjusted-$R^2 = 34.5\%$). Ciclosporin dose (coef = 0.015, $p = 0.043$) and prednisolone dose (coef = -0.38, $p = 0.003$) are maintained within the model with similar coefficients and p-values. Weight and azathioprine dosage were lost from the model and replaced by duration of the transplant (coef = 0.07, $p = 0.012$) and periodontal bleeding index (coef = 13.41, $p < 0.0001$).

Discussion

The findings from this study illustrate that drug-induced gingival overgrowth remains a significant problem in patients medicated with ciclosporin 16 of the 100 patients having gingival overgrowth scores of 30% or greater. However, the proportion of patients with clinically significant changes is lower than reported in previous studies for patients medicated with ciclosporin alone (Thomason et al. 1995, 1996). It is not possible to determine from these data if this is as a result of the change to the newer formulation of ciclosporin (Neoral™, Novartis Pharmaceuticals Corporation, East Hannover, NJ, USA) for many patients. There were no significant differences between the two groups for any of the non-periodontal variables. This is also reflected in the linear regression modelling and the only variable identified as a risk factor for this condition was the papilla bleeding index.

The majority of patients (89%) were either heart or lung transplant recipients and 82% were more than 6 months post-transplant. Use of calcium channel blockers prior to transplantation is very speculative. Since the prevalence of calcium channel blocker-induced gingival overgrowth is low (6%) (Ellis et al. 1999), and resolution occurs following cessation of the drugs, it is highly unlikely that any patients medicated with calcium channel blockers prior to transplantation would continue to demonstrate significant gingival changes attributable solely to those drugs at the time of the investigation.

Univariate regression modelling the gingival overgrowth score as the dependent variable identified a number of independent variables as risk factors. These included duration of therapy, creatinine serum concentration and the papilla bleeding index, each of which have been suggested as risk factors in earlier studies (Thomason et al. 1995, 1996).

A number of authors have suggested that gingival overgrowth progresses most rapidly in the first 3–6 months and then stabilizes (Daley et al. 1986, Somacarrera et al. 1994a). Indeed, it has been suggested that the lesion may resolve with time, at least in cardiac transplant patients (Montebugnoli et al. 1996). When looking at groups of patients, many of whom will be outside this range, most authors have found no correlation between gingival overgrowth and the duration of therapy (Pernu et al. 1992b, King et al. 1993, Pernu et al. 1993, Wondimu, et al. 1993, Vescovi et al. 1997, Thomas et al. 2001). Although at some stage there has to be a levelling off of gingival overgrowth development, the positive relationship between duration of therapy and the severity has been a consistent finding by our research group using the methodology described here. It is perhaps the sensitivity of the overgrowth assessment method, and wide variation in the time that patients have been medicated for in the study, that continues to allow us to demonstrate this relationship.

The inverse relationship seen between creatinine serum concentration and the severity of the changes in the univariate analysis may at first appear a little obscure but is in accord with earlier findings. The concentration of creatinine in the serum was lower in patients with clinically significant overgrowth, and the regression analysis suggests that high serum creatinine levels are protective against gingival changes. Increased creatinine levels have been reported in patients medicated with ciclosporin alone compared with those concomitantly medicated with calcium channel blockers (Thomason et al. 1996). This may be because of an intrinsic mechanism involving creatinine itself, or may reflect the nephrotoxicity of ciclosporin and the amelioration provided by calcium channel blocking drugs in patients taking these drugs concomitantly. Increased creatinine levels are a sign of renal failure and consequent uraemia (Dobbelstein 1976). The latter leads to reduced immunocapacity and weakened inflammatory responses (Rebuck et al. 1971). This may suggest an explanation

for the relationship between high creatinine concentrations and lower overgrowth scores (Thomason et al. 1994). Equally, as creatinine levels are used clinically to monitor renal function, raised creatinine levels may simply be a surrogate for changes in renal function that may themselves affect the pharmacokinetics of ciclosporin and the development of overgrowth. More simply, it may reflect the practice of physicians managing these patients to lower ciclosporin medication in patients who experience increased creatinine levels.

Both final models contain ciclosporin dose as risk factors. In accord with most other reports, this has not been shown in our studies before, possibly because of the synergistic effect of calcium channel blockers on the gingival changes. The role of ciclosporin dosage and blood levels has been widely speculated upon. It was postulated that a dose reduction plays a role in the reduction of gingival overgrowth (Saravia et al. 1990, Daly 1992). These reports lent some support to the concept of a threshold effect, proposed by Daley et al. (1986), although they and most other groups have been unable to detect any correlation between dosage of ciclosporin and gingival overgrowth (for review see Seymour & Jacobs 1992). The scenario for ciclosporin blood concentrations is very similar, nevertheless, three longitudinal studies from the late 1980s and early 1990s give support for a positive relationship between ciclosporin blood concentration and dosage and the gingival changes. In a study of 32 child renal recipients, the authors found no relationship between the current ciclosporin dose and gingival overgrowth, except that the total dose of ciclosporin over the first 6 months was significantly higher among patients with gingival overgrowth than those without (Wondimu et al. 1993). This finding supports the earlier report by Seymour et al. (1987), who demonstrated a positive correlation between the mean serum concentration of ciclosporin over the 6 month investigation period, and the increase in gingival overgrowth. Both these reports may be considered with some caution because of the relatively small number of subjects involved (32 and 12 respectively) but they have been substantiated by a larger longitudinal trial involving a total of 100 patients (Somacarrera et al. 1994a). They reported a positive correlation between ciclosporin blood concentrations and gingival overgrowth in the first 6 months post-transplant. Similar results have been reported in animal studies (Seibel et al. 1989). The present study would also suggest that ciclosporin dosage is a risk factor for the severity of the gingival changes. The width of the confidence intervals for the regression coefficient makes it difficult to predict the magnitude of the effect with any degree of certainty, but using the coefficient itself would suggest that a doubling of the dosage from 200 to 400 mg/day would increase the overgrowth score by less than 4 units. It is perhaps because of the size of the confidence interval that this relationship has not been demonstrated in many previous studies, where its consequence has been masked by the much larger synergistic effect of the calcium channel blockers.

By contrast, the relationship with gingival inflammation remains by far the most robust, but the size of its effect is approximately the same as that for ciclosporin dosage. Changes in the papillary bleeding index representing the differences in the interquartile range of values for the study predict changes in the overgrowth score of 4–5 units. The positive relationship between inflammation and gingival overgrowth is widely accepted (for review see Seymour et al. 1996). However, in cross-sectional studies, while it is possible to show a significant relationship between gingival inflammation and the severity of gingival overgrowth, it is never possible to identify which side of the relationship is causal. Nevertheless, in circumstances when other additional structures such as orthodontic appliances impede cleaning, the prevalence of overgrowth is high (Daley et al. 1991), and equally, the magnitude of gingival changes were shown to be less in patients enrolled on an oral hygiene programme (Seymour & Smith 1991). A reduction in the severity of gingival overgrowth and the need for surgery has been reported following an oral hygiene programme (Kantarci et al. 1999). It is, therefore, reasonable to suggest that improved oral hygiene may at least minimize the severity of gingival overgrowth, if by no other means than that of removing the inflammatory component of the lesion. In addition, it would appear that both the anti-inflammatory agents: prednisolone and azathioprine may offer some protection against the development of gingival overgrowth. The regression coefficient for prednisolone was similar in the univariate and multivariate models. The models predict that increasing the prednisolone daily dosage by 5 mg (the interquartile range) would reduce the overgrowth score, again by some 4–5 units. The regression coefficient for azathioprine was much smaller (coef = -0.05); however, the patients are medicated with a wide range of doses. The same calculation for azathioprine suggests a reduction of a similar magnitude. Azathioprine was excluded from the final model containing the periodontal variables. In essence, therefore, once adjusted for the effect of other variables in the model, the addition of azathioprine did not add separate information on the variability of the dependent variable. The selection of predictor variables for a model is affected by the degree of correlation between the variables themselves, and highly correlated pairs are usually not both included unless they offer separate information (Altman 1991). The impact of changes in prednisolone and azathioprine dosage may be manifested directly by their anti-inflammatory properties. If this were the case, then replacement of azathioprine by papilla bleeding index in the final model is to be expected and supports the role of inflammation as a true risk factor for gingival overgrowth.

It has also been suggested that azathioprine may exert its effect because of the possibility of reducing the ciclosporin medication in patients medicated with azathioprine (Wilson et al. 1998). Although some of the patients in their study were not medicated with ciclosporine, perhaps clouding the issue a little, the general findings are supported by an earlier report suggesting that patients medicated with azathioprine had lower gingival overgrowth scores than those not taking azathioprine (Somacarrera et al. 1994a). The authors postulate, that this was related to lower ciclosporin blood concentrations in the azathioprine group, and is supported by the present study. Patients medicated with either azathioprine or prednisolone have significantly lower ciclosporin dosages and blood levels. The impact of changes in prednisolone and azathioprine dosage may thus be manifested either directly by their anti-inflammatory properties, or through their effect on ciclosporin pharmacodynamics and kinetics.

Conclusion

Patients medicated with ciclosporin are at risk of clinically significant gingival overgrowth. The dosage of each of the three immunosuppressants considered was identified as risk factors for the severity of the gingival change. This observation has not been seen in earlier studies that included many patients concomitantly medicated with calcium channel blockers. In these other studies, the effects of the dosage of the three immunosuppressants may simply have been masked by the synergistic effects of the calcium channel blockers.

The explanatory models in this study contain a number of variables that moderate inflammation (azathioprine and prednisolone) or are markers of it (papilla bleeding index). The loss of azathioprine from the final model in favour of the periodontal bleeding index and the absence of plaque score from any of the models further highlight the prime role of inflammation in this condition.

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