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Effectiveness of periodontal therapy on the severity of cyclosporin A-induced gingival overgrowth

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Abstract

Aim: The purpose of the present study was to evaluate the clinical effects of aetiological periodontal treatment in a group of transplant patients medicated with cyclosporin A (CsA) who exhibited severe gingival overgrowth.

Materials and Methods: Twenty-one patients received oral hygiene instructions, supra- and subgingival scaling and periodontal maintenance therapy and were monitored for 12 months. Full-mouth plaque score (FMPS), full-mouth bleeding score (FMBS), periodontal probing depth and degree of gingival overgrowth (Seymour index GO) were recorded at baseline, 6 and 12 months after treatment.

Results: Statistical evaluation revealed that all clinical variables significantly decreased compared with baseline. At baseline 18 out of 21 treated patients (85.71%) exhibited clinically significant overgrowth. Initial GO score of 2.38 ± 1.92 in the anterior sextants and of 1.29 ± 1.59 in the posterior segments were reduced to 0.56 ± 0.83 and to 0.45 ± 0.84 at 12 months ($p < 0.001$). A difference of 1.82 and 0.84 in the severity of treated GO was accompained by a 42% and 34% decrease in FMPS and FMBS, respectively.

Conclusions: Aetiological periodontal treatment and regular maintenance therapy were effective in resolving the inflammation and in eliminating the need for surgical treatment in patients receiving CsA.

Key words: aetiological periodontal treatment; cyclosporin A/adverse effects; gingival overgrowth/aetiology

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Gingival enlargement represents one of the various unwanted side effects of cyclosporin A (CsA) therapy (Seymour & Jacobs 1992). The incidence of gingival overgrowth (GO) among transplant patients treated with CsA ranges from 6% to 81% (Pernu et al. 1992, Dongari et al. 1993, Somacarrera et al. 1994). Such a variation in individual susceptibility can be as a result of the great number of inter-patient variables such as dosage, duration of CsA treatment, concomitant use of other drugs, age, immunological changes, genetic pre-disposition, systemic diseases and level of plaque control (Somacarrera et al. 1994, Seymour et al. 1996, Seymour et al. 2000).

The importance of the bacterial biofilm in the aetiology of GO has been extensively studied. However, no clear correlation between plaque-induced gingival inflammation and development of cyclosporin-mediated GO has been established (Somacarrera et al. 1994, Pilatti & Sampaio 1997, Afonso et al. 2003, Romito et al. 2004). In addition, there is no agreement in the literature about the effects of home and professional plaque control on gingival enlargement. Several authors have observed a positive association between an intensive oral hygiene programme, supra- and subgingival scaling and improvement of CsA GO (Darbar et al. 1996, Somacarrera et al. 1997, Santi & Bral 1998, Kantarci et al. 1999), while others failed to confirm this (Seymour & Smith 1991, Pernu et al. 1993, Montebugnoli et al. 1996). As regards the time-related effectiveness of initial periodontal therapy, except for the study by Santi & Bral (1998), there are no investigations that have analysed the response of CsA overgrown gingival tissues for more than 6 months, or they have focused their attention on the anterior segments.

Therefore, the aim of the present study was to evaluate the 12-month clinical effects of aetiological periodontal treatment and maintenance therapy in transplant patients who

exhibited clinically evident CsA-induced GO.

Materials and Methods

Patients selection and assessment of periodontal status

Twenty-one organ transplant patients (five women and 16 men; mean age 51.95 ± 13.19 years, range 25–66 years) were consecutively scheduled for the present study among patients who were referred for CsA-induced GO to the Division of Periodontics at the Dental School of the University of Torino. Eleven individuals had received kidney transplants, five had received liver transplants and five had received heart transplants. Patients had been on a CsA immunosuppression regimen (Sandimmun Neoral®, Sandoz Wander Pharma S.A., Brunnmatstrasse, Berna, Switzerland) for an average of 7.86 (range 3–14) years with dosages between 125 and 400 mg/day (mean 215.48 ± 89.26). The mean whole-blood level of CsA was 147.14 ± 67.88 ng/ml. One liver recipient and one heart transplant patient were medicated with the combination of CsA and corticosteroids (5 and 10 mg/day). In seven renal transplant recipients, CsA was supplemented with corticosteroids (2.5–10 mg/day) and azathioprine (50–75 mg/day) and in one with azathioprine, depending on the medical protocol for transplant. The conversion from azathioprine to mycophenolate mofetil was carried out in three kidney patients because of myelotoxic side effects of the drug.

All patients were non-smokers, did not receive any periodontal treatment during the post-transplantation period, did not have any systemic disease reported to cause GO and any bone resorption as diagnosed by serial radiographs and clinical evaluation. Informed consent was obtained from each patient prior to the investigation, and the protocol was approved by the Ethical Committee of the Medical Faculty, University of Torino.

At initial examination (baseline), the periodontal evaluation included assessment of full-mouth plaque score (FMPS), full-mouth bleeding score (FMBS) and probing depth (PD) recorded by means of a Williams 0 probe (Hu-Friedy, Chicago, IL, USA) at six points around each tooth. All clinical recordings were performed by the same investigator throughout the study.

The degree of GO was graded numerically on a plaster study model using the scoring method described by Seymour et al. (1985). This was expanded to allow recordings of all inter-dental sites, not just those of upper and lower anterior segments (canine to canine). A GO score was assigned to each inter-dental papilla (gingival unit) and it was the sum of two components. The first component measured the degree of gingival thickening labially and lingually by means of a three-point scale (0 = normal width, 1 = thickening up to 2 mm, 2 = thickening of more than 2 mm). The second component measured the extent of encroachment of the gingival tissues on the labial and lingual aspects of adjacent tooth crown and it ranged from 0 (no clinical evidence of overgrowth) to 3 (overgrowth covering three-fourths of tooth crown). The papilla distal to the last-standing molar and points with an adjacent edentulous space were not measured.

The GO scores were recorded separately for the anterior and posterior segments. They were expressed as mean standard deviation for the anterior and posterior teeth, and for the anterior gingival units, were also expressed as percentage (Seymour et al. 1985). Patients with a GO score $>30\%$ were regarded as responders (Thomason & Seymour 1990, Seymour & Smith 1991). Furthermore, we measured the degree of gingival enlargement in the apico-coronal direction as distance in millimetres from the mucogingival junction to the base (MGJ–B) and to the apex of all inter-dental papillae (MGJ–A).

Periodontal therapy

At the beginning of the study, after recording baseline parameters, patients underwent oral hygiene instructions, supra- and subgingival scaling with ultrasonic and hand instruments. The difficulty in accomplishing an effective home plaque control because of the distorted contours of overgrown gingival tissues required instructions in the oral hygiene techniques and devices more suitable for individual anatomical features and frequent controls during scaling sessions and recall appointments.

All treatments were carried out under antibiotic coverage (amoxycillin 2 g 1 h pre-operatively) as recommended by organ transplant centres because of patients' increased susceptibility to infections (Guggenheimer et al. 2005).

After completion of aetiological periodontal therapy, patients were placed on a recall maintenance programme and monitored for 12 months. Maintenance therapy included re-inforcement of oral hygiene instructions and full-mouth scaling every 2 months.

All the patients were re-evaluated at 6 and 12 months, and periodontal variables were recorded.

Statistical analysis

The experimental unit in statistical analyses of GO, MGJ–A and MGJ–B was the inter-dental papilla, while with regard to PD, the mean score of the six values recorded around each tooth was taken for calculation. The Bonferroni test and the Dunn's test were used to compare the differences between basal, 6-month and 12-month values for PD and GO, respectively. For analysing the changes of MGJ–A and MGJ–B, the one-way ANOVA and Tukey's test were used and for FMPS and FMBS, Student t test for paired samples were used. $p<0.05$ was the critical value.

Results

All patients completed the study. At baseline, 18 out of the 21 patients (85.71%) had clinical GO (GO$\geqslant$30%) and were regarded as responders.

In total, 507 teeth and 834 gingival units were assessed. Two hundred and seventy-two gingival units among 352 examined in the anterior segments (77.27%) and 261 among 482 assessed in the posterior area (54.15%) were overgrown, with an average GO score of 2.38 ± 1.92 (40.81 ± 17.1%) and 1.29 ± 1.59, respectively. The severity of GO of affected sites as measured by Seymour's index is presented in Tables 1 and 2.

All patients exhibited a number of overgrown gingival units with a score of grade 1 in the posterior segments, and 19 participants (90.5%) in the anterior region as well. Nineteen patients (90.5%) presented sites with a score of 2–3 in the anterior sextants and 17 (80.9%) in the posterior ones. In addition, 18 individuals (85.7%) had almost one gingival unit in the anterior region and 12 (57.1%) in the pre-molar and molar region with a GO score of 4–5.

Table 1. Severity of gingival overgrowth (GO) according to Seymour's index in the anterior segments at baseline (T0), 6 months (T6) and 12 months (T12)

GO score	T0		T6		T12	
	no. of patients (%)*	no. of gingival units (%)†	no. of patients (%)*	no. of gingival units (%)†	no. of patients (%)*	no. of gingival units (%)†
0	21 (100)	80 (22.7)	21 (100)	183 (52)	21 (100)	213 (60.5)
1	19 (90.5)	56 (15.9)	20 (95.2)	86 (24.4)	19 (90.5)	88 (25)
2	19 (90.5)	61 (17.3)	18 (85.7)	52 (14.8)	16 (76.2)	40 (1.4)
3	17 (80.9)	33 (9.4)	13 (61.9)	27 (8.3)	12 (57.1)	10 (2.8)
4	16 (76.2)	31 (8.8)	2 (9.5)	3 (0.8)	1 (4.8)	1 (0.3)
5	18 (85.7)	91 (25.8)	1 (4.8)	1 (0.3)	0 (0)	0 (0)

*Percentage of total group.
†Percentage of total gingival units examined.

Table 2. Severity of gingival overgrowth (GO) according to Seymour's index in the posterior segments at baseline (T0), 6 months (T6) and 12 months (T12)

GO score	T0		T6		T12	
	no. of patients (%)*	no. of gingival units (%)†	no. of patients (%)*	no. of gingival units (%)†	no. of patients (%)*	no. of gingival units (%)†
0	20 (95.2)	221 (45.8)	21 (100)	317 (65.8)	21 (100)	345 (71.6)
1	21 (100)	103 (21.4)	20 (95.2)	67 (13.9)	20 (95.2)	78 (16.2)
2	17 (80.9)	49 (10.2)	14 (66.7)	50 (10.4)	11 (52.4)	39 (8.01)
3	14 (66.7)	44 (9.1)	10 (47.6)	35 (7.3)	9 (42.8)	17 (3.5)
4	12 (57.1)	31 (6.4)	4 (19)	12 (2.5)	1 (4.8)	3 (0.06)
5	10 (47.6)	34 (7)	1 (4.8)	1 (0.2)	0 (0)	0 (0)

*Percentage of total group.
†Percentage of total gingival units examined.

Table 3. Clinical parameters assessed at baseline (T0), 6 months (T6) and 12 months (T12) post-operatively

	T0	p^* (T0–T6)	T6	p^* (T6–T12)	T12	p^* (T0–T12)
FMPS	56.47 ± 18.17	0.000 (a)	13.52 ± 2.84	NS§ (a)	14.06 ± 1.91	0.000 (a)
FMBS	49.2 ± 24.37	0.000 (a)	14.96 ± 4.08	NS§ (a)	14.91 ± 2.19	0.000 (a)
GO ant	2.38 ± 1.92	<0.001 (b)	0.77 ± 1.00	<0.05 (b)	0.56 ± 0.83	<0.001 (b)
GO post	1.29 ± 1.59	<0.001 (b)	0.66 ± 1.08	<0.001 (b)	0.45 ± 0.84	<0.001 (b)
PD	3.9 ± 1.4	<0.0001 (c)	2.2 ± 0.93	NS§ (c)	2.1 ± 0.86	<0.0001 (c)
MGJ–A	8.3 ± 2.3	0.0001 (d)	5.9 ± 1.6	NS§ (d)	5.6 ± 1.44	0.0001 (d)
MGJ–B	4.9 ± 3.9	0.0001 (e)	3.5 ± 1.1	NS§ (e)	3.3 ± 0.9	0.0001 (e)

FMPS, full-mouth plaque score; FMBS, full-mouth bleeding score; GO ant, gingival overgrowth score assessed in the anterior segments; GO post, gingival overgrowth score assessed in the posterior segments; PD, probing depth; MGJ–A, distance between the mucogingival junction and the apex of all interdental papillae; MGJ–B, distance between the mucogingival junction and the base of all interdental papillae.
Results are expressed as mean ± SD: (a) Student's *t* test for paired samples; (b) Dunn's test; (c) Bonferroni's test; (d) one-way ANOVA; (e) Tukey's test.
*Statistically significant at $p<0.05$.
§NS, not statistically significant.

Using our original scoring method, the mean of MGJ–B and MGJ–A was 4.9 ± 3.9 and 8.3 ± 2.3 mm, respectively (Table 3).

At 6 months, all treated subjects responded well to the periodontal therapy and had GO scores <30% (mean 13.29 ± 7.14%). In the anterior teeth, 52% of gingival units were still not affected (Table 1) and 65.8% in premolar and molar regions (Table 2), with a statistically significant decrease of GO to 0.77 ± 1.0 and 0.66 ± 1.08, respectively ($p<0.001$). The lowering of the GO scores was accompanied by the reduction of MGJ–A and MGJ–B values to 5.9 ± 1.6 and to 3.5 ± 1.1 mm with a statistically significant difference compared with baseline ($p<0.0001$).

All periodontal parameters (FMPS, FMBS, PD) decreased significantly as a result of the therapy during the course of the study (Table 3). At 6 months after periodontal treatment, the decrease in FMPS and FMBS from 56.47 ± 18.17% to 13.52 ± 2.84% and from 49.20 ± 24.37% to 14.96 ± 4.08% was statistically significant ($p<0.0001$) with respect to baseline. The improvement in PD values from 3.9 ± 1.4 mm at baseline to 2.2 ± 0.93 mm was also statistically significant ($p<0.0001$).

At 12 months post-therapy, the MGJ–A, MGJ–B and PD scores were quite similar (Table 3), while a significant reduction of GO was observed in the anterior ($p<0.05$) and posterior segments ($p<0.001$). At the end of the observation period, all 21 treated

patients showed a decrease in GO scores ($0.56 \pm 0.83\%$ and $9.57 \pm 5.71\%$ in the anterior segments and 0.45 ± 0.84 in the posterior sextants) and only two had four gingival units with scores of grade 4. In the anterior teeth 60.5% (Table 1) and in the posterior regions 71.6% of the gingival units were still not affected (Table 2).

Discussion

The results of our study demonstrated that proper self-performed supragingival plaque control combined with professional subgingival instrumentation are effective in the treatment of gingival enlargement in transplant patients medicated with CsA. At the end of the observation period, the GO score decreased by 1.82 from a baseline value of 2.38 in the anterior sextants and by 0.84 from a baseline score of 1.29 in the posterior segments. None of the 18 patients regarded as responders had GO > 22% and gingival units with a score of 5 in the anterior and posterior segments. In addition, in one case a complete regression of gingival enlargement was observed. The marked reduction in the number of affected sites (-66.9%) was accompanied by a simultaneous decrease in gingival inflammation and plaque by 34% and 42%, respectively.

Few data have been published on this subject. The best available evidence of the aetiological periodontal treatment on CsA GO so far derives from investigations that presented data at 8 weeks (Kantarci et al. 1999) and 6 months (Somacarrera et al. 1997) post-operatively, and evaluated the clinical response only of the anterior segments. In contrast with the above-mentioned investigations, we analysed the gingival changes that occurred not only in the anterior sextants but also in the posterior areas, extending the index described by Seymour to all the inter-dental papillae. In agreement with the overall picture of the distribution of gingival enlargement, the number of affected inter-dental sites was higher in the anterior segments than in the posterior areas, and the most pronounced gingival enlargement was located on the labial gingiva in the incisive and canine region (Thomason et al. 1996). Additionally, we measured not only the amount of gingival thickening (buccolingually) and gingival encroachment (mesiodistally) but also the apicocoronal dimension of gingival enlargement from the mucogingival junction to the base and apex of each labial papilla. We observed a statistically significant reduction of MGJ–A and MGJ–B values from 8.3 ± 2.3 to 5.9 ± 1.6 mm and from 4.9 ± 3.9 to 3.5 ± 1.1 mm in the first 6 months, which remained fairly unchanged during 6–12 months.

The data presented in our examination were better than those published by Kantarci et al. (1999), who observed approximately 40% improvement in GO and inflammation values and suspension of clinically significant enlargement in 47% of patients.

The differences in the experimental design might partly account for these discrepancies. Initially, our patients received maintenance therapy, which is important to prevent or reduce the recurrence of GO, as previously demonstrated (Echeverria et al. 1996, Ilgenli et al. 1999). In addition, Kantarci et al. investigated the 8-week clinical response of overgrown gingiva following aetiological treatment. An 8-week study is probably too brief to evaluate changes in gingival volume, which take longer to show a significant improvement (Montebugnoli et al. 2000). In fact, in our 1-year clinical trial, the most beneficial effects occurred within the first 6 months post-treatment and were followed by a period of stability attributable to a re-inforcement with time of the oral hygiene programme and to maintenance scaling. The only parameter that showed a continued decrease over the 12-month period was GO. This finding is in agreement with the soft-tissue behaviour following periodontal treatment. After an initial phase of healing, the maturation of soft tissues occurs within several months.

These observations support the importance of a carefully monitored, but self-performed plaque control programme and frequent recall appointments. Instructions and motivation to proper oral home care measures, incorporated in an aetiological therapy programme are the basic aspects in the clinical management of transplant patients exhibiting CsA-induced GO. This phase can be very complex in these patients because of local anatomic features and poor compliance. In the literature, there is no consensus on the role of supragingival plaque control in the treatment of CsA gingival enlargement. In fact, some investigators have suggested oral hygiene programme as a routine approach to prevent or reduce gingival enlargement after transplantation (Rateitschak-Plüss et al. 1983, King et al. 1993, Thomason et al. 1993, Somacarrera et al. 1994), while others claimed that plaque control was effective only to a limited extent in the management of CsA GO (Friskopp & Klintmalm 1986, Seymour & Smith 1991, Montebugnoli et al. 1996). In the present trial, home plaque control has been associated with professional removal of local irritants through supra- and subgingival debridement and maintenance scaling. Plaque elimination through oral home care measures is probably not capable of controlling the severity of gingival enlargement alone, as demonstrated by Kantarci et al. (1999). Changes in gingival contours allow accumulation of significantly more dental plaque and calculus beneath the overgrown tissue than does the normal gingival tissue. In addition, effective mechanical plaque removal is more difficult to accomplish. It has been demonstrated that dental floss, toothbrushes and other hygiene aids can reach only a limited distance below the gingival margin (Waerhaug 1981), and are effective only in shallow and moderately deep pockets (Greenstein 1992, Sato et al. 1993). In the present investigation, patients were instructed in the use of toothbrushing methods and oral hygiene devices more suitable for their gingival features, and their plaque control was carefully supervised. The achievement of a high quality of home plaque control, with an FMPS of about 10–15% seems to be essential for the long-term stability of clinical improvements.

Our data provide further evidence that the severity of gingival enlargement is related to the plaque-induced gingival inflammation, and that plaque is a cofactor in the aetiopathogenesis of CsA-induced GO (Fu et al. 1997). This is supported by the observation that approximately 40% of the CsA gingival enlargement can be considered to be of inflammatory nature (Hassell & Hefti 1991, Kantarci et al. 1999), and that drug sequestration in gingival crevicular fluid is greater in the inflamed compared with non-inflamed sites (Ellis et al. 1995). In addition, the plaque may act as a reservoir, slowly releasing CsA and maintaining the deleterious effect on gingival tissues (Niimi et al. 1990).

On the basis of these findings, we suggest that oral hygiene phase and root surface instrumentation should be the

first step in the management of GO as well as in any periodontal treatment plan. This conservative approach decreases the need for surgical therapy, which is often followed by a recurrence of severe GO (Pernu et al. 1993, Ilgenli et al. 1999). Furthermore, the critical score of GO that warrants surgical correction is disputable (Seymour et al. 1985, Pernu et al. 1993, Inglés et al. 1999). In light of our experience, we believe that the decision for surgical intervention should be taken after aetiological periodontal treatment and at least a 12-month maintenance therapy. In addition, we suggest that the degree of GO that requires surgical treatment should be evaluated in accordance with individual functional and aesthetic requirements. Effective oral hygiene procedures are more difficult to accomplish in the presence of distorted gingival contours. In such cases, surgical restoration of gingival margin may be indicated.

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