Regina Purschwitz, Hannelore Schmidt, Holger Jentsch

Ciclosporin A-induced gingival enlargement. Clinical and microbiological modifications after conversion to the medication tacrolimus: an account of ten patient cases

Regina Purschwitz

Hannelore Schmidt

Holger Jentsch

All three:
University of Leipzig,
Centre for Dentistry and
Oral Medicine,
Polyclinic for Preservative
Dentistry and
Periodontology,
Nürnberger Strasse 57,
04103 Leipzig,
Germany

Uta Wesiger
Private practice,
Pestalozzistrasse 16,
04747 Hartha,
Germany

Correspondence to:
Regina Purschwitz
Polyclinic for Preservative
Dentistry and
Periodontology,
Nürnberger Strasse 57,
04103 Leipzig,
Germany
Email: regina.purschwitz
@medizin.uni-leipzig.de

KEY WORDS *ciclosporin A, gingival enlargement, subgingival biofilm, tacrolimus*

The objective of the investigation was to assess changes of periodontal variables, particularly the gingival width, hyperplasia index and the subgingival flora, after changing medication from ciclosporin A to tacrolimus. Ten patients with gingival enlargement were included in the study. Plaque index, gingival index and hyperplasia index together with papillary and marginal gingival width were measured immediately after the change-over as well as after 4, 8 and 26 weeks. At the beginning and end of the investigations, probing depths were determined and subgingival plaque samples were assessed using polymerase chain reactions to *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, *Eikenella corrodens*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Treponema denticola* and Capnocytophaga. Significant improvements were found in the probing depth, the hyperplasia index and the papillary gingival width after 8 and 26 weeks as well as in the marginal gingival width after 8 weeks. *T. forsythia* was significantly reduced at the end of the study into subgingival plaque. The change in medication from ciclosporin A to tacrolimus had positive effects on clinical variables and the subgingival biofilm.

■ Introduction

Ciclosporin A (Sandimmune®, Novartis Pharma, Nuremberg, Germany) is an immunosuppressive medication, which is used to treat immune-mediated diseases and has been used to prevent and treat transplant rejections in Germany since 1983, as well as to control the graft-versus-host reaction in transplant medicine. Despite the apparent successes and advantages of this medication, a number of side effects such as hepatotoxicity, nephrotoxicity and neurotoxicity, hypertension, hyperlipidaemia and susceptibility to viral, bacterial and fungal infections have been described. Another significant side effect is the occurrence of gingival enlargement[1]; prevalence in adults is between 8% and 81%[2]. The considerable range of fluctuation can be explained mainly by individual susceptibility[3]. Tissue changes arise predominantly through an addition of extracellular matrix and are not caused by a size increase or cell proliferation of the fibroblasts. Instead of the terms 'hyperplasia' or 'hypertrophy', the term 'gingival enlargement' is preferred[3,4].

The increased probing depths caused by the tissue enlargement are connected with considerable

amounts of plaque; in addition, the gingiva exhibits distinct inflammation. Microbiological analyses[5,6] have shown bacterial settlement of these pockets in relation to the enlargement.

From studies concerning the relationship between the development of gingival enlargement and factors such as dosage, plasma concentration, additional medication and plaque control, varying results have been reported[7-9]. Many authors advocate a multi-factorial pathogenesis model[2,10,11].

In 1995, the immunosuppressive medication tacrolimus (FK 506, Prograf®, Fujisawa Deutschland, Munich, Germany) was introduced in Germany[12]. It inhibits interleukin-2 synthesis in a similar way to ciclosporin A, as well as inhibiting the production of T lymphocytes. However, it has up to a 100 times stronger immunosuppressive effect[12]. The field of application is basic immunosuppression in transplant medicine as well as the treatment of acute transplant rejections. Known side effects are, predominantly, hyperglycaemia, nephrotoxicity and gastrointestinal problems[13]. During the primary administration of tacrolimus after organ transplantation, no changes to the gingiva have been detected to date[14,15]. The remission of gingival proliferation after the change in medication from ciclosporin A to tacrolimus seems to be safe. In addition, individual case reports[12,16,17] and observations exist from a transplant medical point of view[18,19]. In some cases, the changes were described using indices[17,19]. Eger et al[20] reported measurements of the mucous membrane thickness. They found a high validity for the thickness measurement with an ultrasonic device (SDM, Krupp, Essen, Germany) for periodontally healthy probands. To date, differentiated measurements of change with this device in connection with medication administration have not been shown.

The objective of this investigation was to examine effects on periodontal health of changing medication from ciclosporin A to tacrolimus. Changes in the periodontal variables, gingival enlargement and the subgingival microflora were examined over a period of 26 weeks after changing the medication.

■ Study design

Ten patients, who had been immunosuppressed after kidney or liver transplantations with ciclosporin A, were included. As well as gingival enlargement, all of the patients exhibited other side effects, such as hypertension and hyperlipidaemia. Through the Surgical Clinic and Polyclinic at the University of Leipzig, a change in immunosuppressant from ciclosporin A to tacrolimus was undertaken. The patients consented to take part in the change and the investigation, and the ethics commission approved the study design. Patients, who had received ciclosporin A for at least 6 months and who did not take any additional anticonvulsant medication were included.

As drug-related gingival enlargement is significantly stronger on the anterior teeth than on the lateral teeth[9], existence of at least eight anterior teeth was a criterion for inclusion. After agreement with the transplantation centre, the patients received a prophylactic dose of antibiotics for the baseline and exit analyses. On the day of the change-over, as well as 4, 8 and 26 weeks after, the following clinical variables were recorded:

- PI = plaque index in accordance with Silness and Löe[21] on the buccal and lingual surfaces of all teeth
- GI = gingival index in accordance with Löe[22] on four surfaces per tooth (facial, mesiofacial, lingual, mesiobuccal)
- HI = hyperplasia index[23] in accordance with Mutschelknauss on the buccal and lingual surfaces of all teeth

  Level 0: no hyperplastic change of interdental papilla, the free gingiva or the gingiva propria

  Level 1: isolated hyperplasia of the interdental papilla

  Level 2: hyperplasia of the interdental papilla and the free gingiva, bulge-like thickening of the gingival edge

  Level 3: hyperplasia of the interdental papilla, the free gingival and the gingiva propria through to a partial or complete overgrowing of teeth
- GWP = gingival width of the vestibular papillary gingiva to the base of the interdental papilla using mucous membrane thickness measuring device (SDM® device)
- GWM = gingival width of the vestibular marginal gingiva median in an interval of 1 mm to the gingival edge using the SDM® device.

The determination of the gingival width took place atraumatically with the SDM® device[20]. This was done by applying the probe head of the device, which was moistened with water or saliva, with slight pressure facially to the gingiva. The system works with ultrasound impulses, which are reflected differently on the tissue structures. The thickness of the mucous membrane is calculated in the device and can be read immediately.

For the base analysis and after 26 weeks, the following variables were recorded:

- probing depth (PD) at six positions per tooth with a North Carolina probe (CP-15, Hu-Friedy, Chicago, USA)
- removal of subgingival plaque samples at four positions per patient for microbiological diagnostics.

The removal took place using sterile paper picks (IS0 50, Orbis Dental, Offenbach, Germany), which were applied for 15 seconds in the depression of defined teeth (first molar in each quadrant; if the tooth was missing, the neighbouring tooth with the larger proliferation was selected) with a base HI ≥ 1. With a semi-quantitative polymerase chain reaction (PCR), the samples were examined for the presence of *Aggregatibacter actinomycetemcomitans* (*A.a.*), *Tannerella forsythia* (*T.f.*), *Eikenella corrodens* (*E.c.*), *Porphyromonas gingivalis* (*P.g.*), *Fusobacterium nucleatum* (*F.n.*), *Prevotella intermedia* (*P.i.*), *Treponema denticola* (*T.d.*) and Capnocytophaga (DiaMAK Immundiagnostik, Leipzig, Germany). The specification of the proof was guaranteed for every diagnostic determination of the relevant type of bacteria through reference strains, which were each carried along from pure cultures in a separate reaction batch in the PCR. In this way, the correct procedure of the PCR and the amplification product could be checked from each patient sample in a semi-quantitative manner. The results of this evaluation are stated as 'bacterial counts per sample' (BCS) and classified into high or low categories. Results with ≤ 10^4 BCS are classed as low and > 10^4 BCS as high.

The statistical evaluation of the data took place using the Friedman-Wilcoxon test, with a significance level of $P \leq 0.05$.

■ Results

The five women and five men had an average age of 47.4 ± 12.2 years. Nine patients had undergone kidney transplants and one patient had undergone a liver transplant. At the time of the medication change-over, the transplants had been 35.2 ± 15.9 months *in situ*. This corresponds to the length of the immunosuppressive treatment with ciclosporin A. Chronic periodontitis of different sizes and severity had been determined in all patients. Table 1 shows the details of the patients. The average values and standard deviations for PI, GI, HI, GWM, GWP and PD are listed in Table 2. The results of the statistical analysis are shown in Table 3. Changes in the PI and GI yielded no significant changes over time. The PD reduced significantly from 4.59 mm to 3.78 mm at the

Table 1 Characterisation of patients.

Patient	Age	Gender	Indication for transplantation	Chronic periodontitis	Ciclosporin A treatment (months)
1	52	F	Renal failure	Moderate	36
2	63	F	Renal failure	Severe	36
3	34	F	Cirrhosis of the kidney	Moderate	48
4	44	F	Renal failure	Moderate	34
5	57	F	Cirrhosis of the kidney	Moderate	60
6	41	M	Cirrhosis of the liver	Moderate	36
7	68	M	Polycystic kidney	Severe	48
8	31	M	Renal failure	Moderate	35
9	47	M	Polycystic kidney	Moderate	12
10	42	M	Renal failure	Severe	7

Table 2 Clinical variables at the points of investigation (mean ± standard deviation).

Variable	Base analysis	4 weeks	8 weeks	26 weeks
Plaque index	1.1 ± 0.5	0.9 ± 0.5	1.0 ± 0.4	1.0 ± 0.6
Gingival index	1.3 ± 0.4	1.1 ± 0.2	0.9 ± 0.2	1.2 ± 0.5
Hyperplasia index	1.1 ± 0.6	0.7 ± 0.4	0.4 ± 0.4	0.3 ± 0.4
Marginal gingival width	1.6 ± 0.5	1.6 ± 0.3	1.3 ± 0.3	1.8 ± 0.4
Papillary gingival width	2.9 ± 0.9	2.5 ± 0.9	2.2 ± 0.7	2.2 ± 0.5
Probing depth	4.6 ± 1.3	–	–	3.8 ± 0.9

Table 3 Statistical analysis (*P* values) of the clinical variables.

Variable	Friedman Test	Wilcoxon Test Base analysis 4 weeks	Base analysis 8 weeks	Base analysis 26 weeks	4 weeks to 8 weeks	4 weeks to 26 weeks
Plaque index	0.626					
Gingival index	0.090					
Hyperplasia index	< 0.001	0.009	0.008	0.005	0.018	0.314
Marginal gingival width	0.002	0.878	0.021	0.169	0.011	0.008
Papillary gingival width	0.006	0.074	0.011	0.037	0.086	0.575
Probing depth				0.011		

end of the observation period ($P = 0.011$). HI was significantly improved in comparison with the baseline analysis after 4 weeks ($P = 0.009$), after 8 weeks ($P = 0.008$), after 26 weeks ($P = 0.005$), as well as in comparison with the results after 4 and 8 weeks ($P = 0.018$). The GWM reduced significantly in comparison with the baseline analysis after 8 weeks ($P = 0.021$) as well as between weeks 4 and 8 ($P = 0.011$), and significantly increased again at the end of the examination ($P = 0.008$). The GWP was reduced between the baseline analysis and week 8 ($P = 0.011$) as well as between the baseline analysis and week 26 ($P = 0.037$).

Both the initial values and the development of the individual values for the hyperplasia index and the gingival width were different in the patients being observed. They are shown for each individual patient in Figs 1 to 3. The localisation of the hyperplasia was different for each individual. Patient 6 had the highest initial values for the HI and gingival width (Fig 4). At the end of the investigation, this patient exhibited a reduction of 30% (GWP) and 45% (HI) for these variables (Fig 5). During the baseline findings, patient 4 exhibited multiple lobate gingival enlargements (Fig 6), which were especially pronounced in the palatal region, and were considerably reduced after 26 weeks (Fig 7).

The results of the microbiological diagnostics are shown for all patients in Table 4. For *A. a.*, there were no changes observed; for *E. c.*, *F. n.*, *P. g.*, *P. i.*, *T. d.* and for the Capnocytophaga group, there were small changes that were not significant. The number of patients with high BCS for *T. f.* decreased significantly from 7 to 2 ($P = 0.025$).

■ Discussion

The aim of the study was to observe clinical and microbiological changes in 10 organ-transplant patients with gingival enlargement over a period of 26 weeks after changing their medication from ciclosporin A to tacrolimus.

The four-level HI in accordance with Mutschelknauss served to record the gingival proliferation. This evaluation was supplemented by measurement of

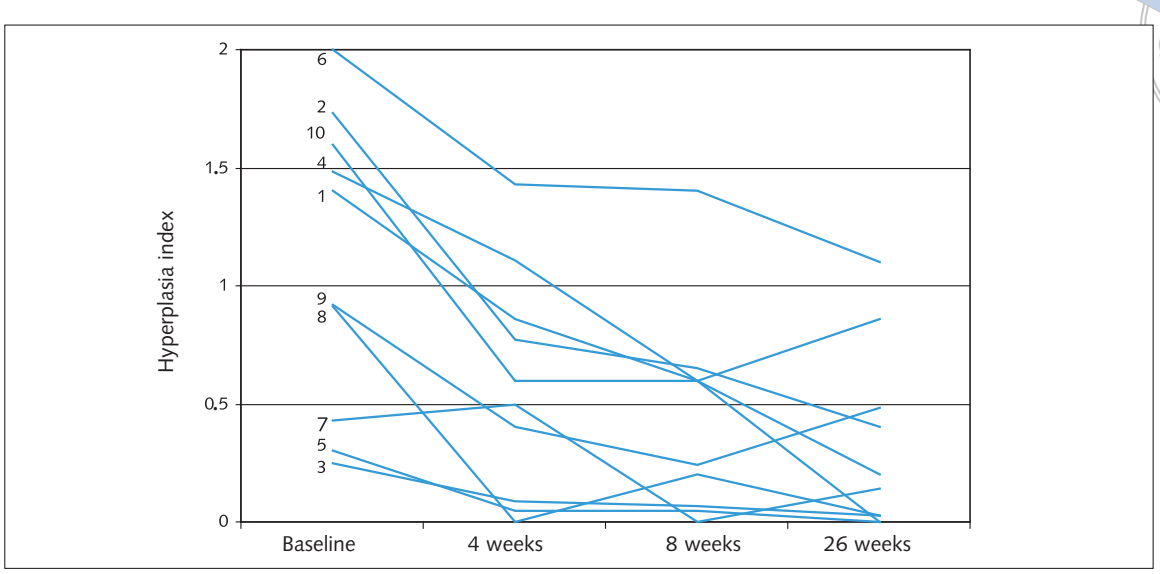

Fig 1 Hyperplasia index (HI) of patients 1 to 10 after changing medication in the investigation period.

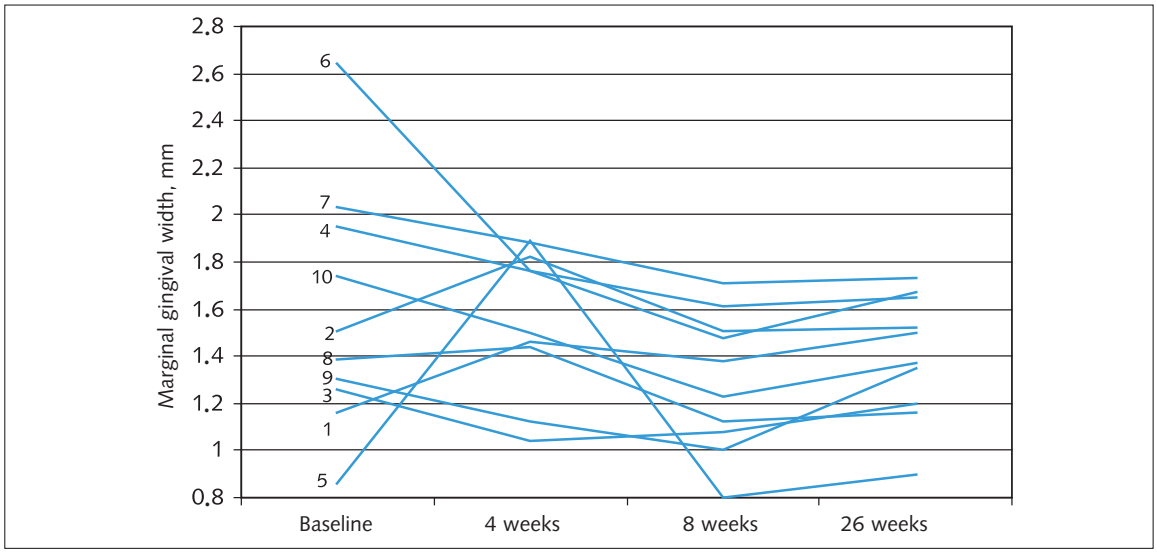

Fig 2 Marginal gingival width (GWM) of patients 1 to 10 after changing medication in the investigation period.

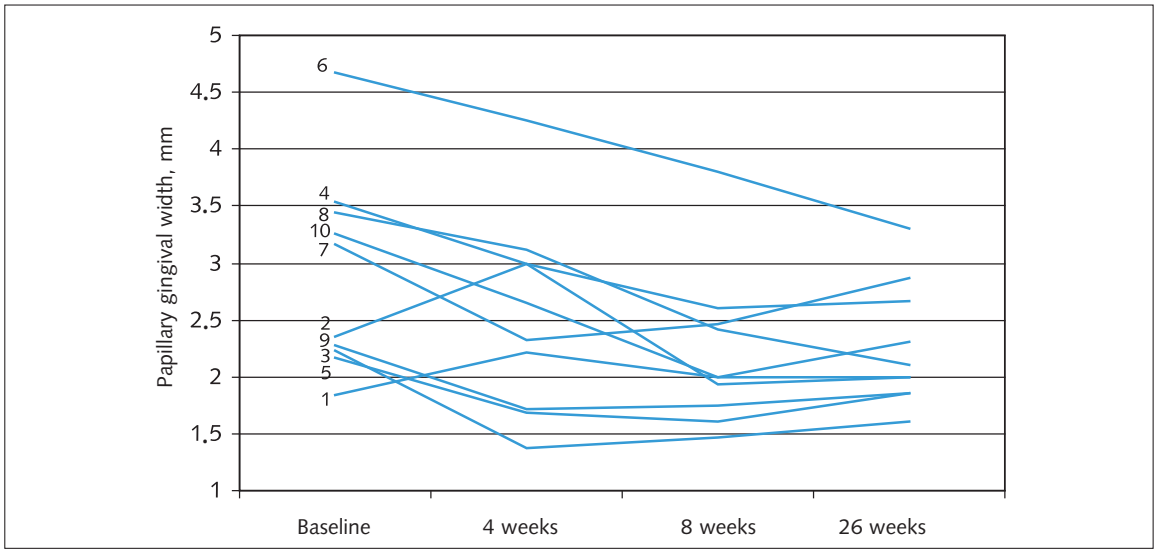

Fig 3 Papillary gingival width (GWP) of patients 1 to 10 after changing medication in the investigation period.

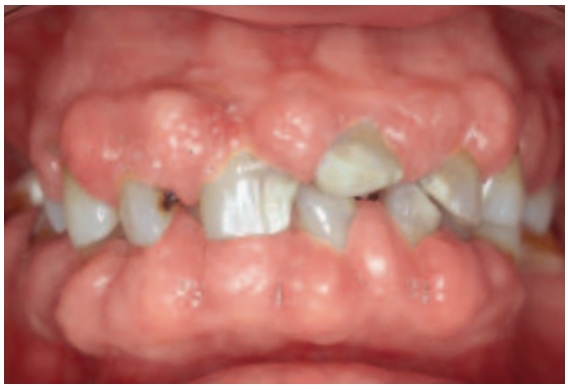

Fig 4 Patient 6, before changing medication.

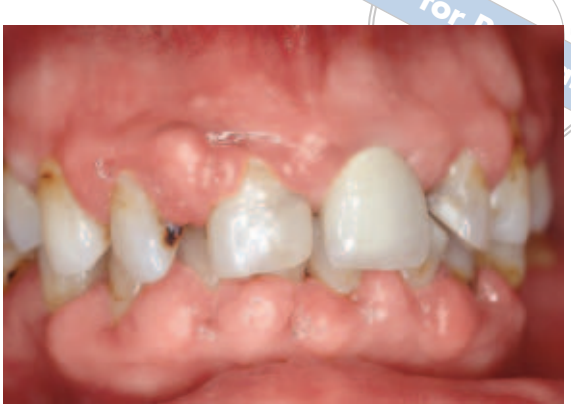

Fig 5 Patient 6, 26 weeks after changing medication.

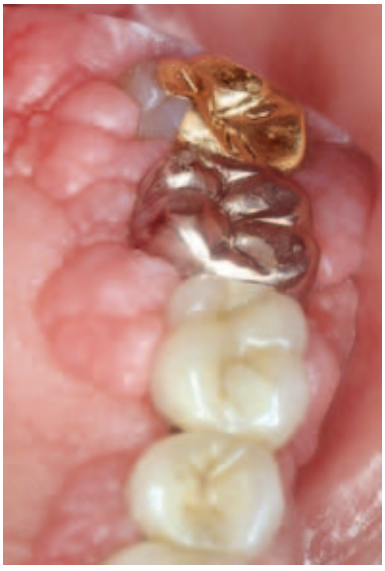

Fig 6 Patient 4, before changing medication.

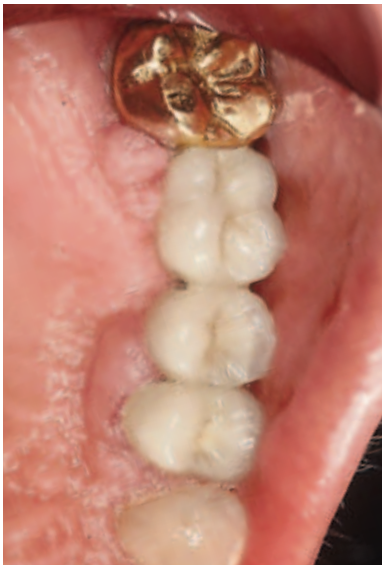

Fig 7 Patient 4, 26 weeks after changing medication.

Table 4 Number of patients with low or high bacterial counts per sample (BCS).

Bacterium	Number of patients				
	Low BCS (≤ 10^4)		High BCS (> 10^4)		
	Base analysis	26 weeks	Base analysis	26 weeks	Wilcoxon Test
A. actinomycetemcomitans	9	9	1	1	0.655
T. forsythia	3	8	7	2	0.025
E. corrodens	6	7	4	3	0.655
F. nucleatum	6	3	4	7	0.257
P. gingivalis	7	8	3	2	0.317
P. intermedia	7	9	3	1	0.317
T. denticola	8	7	2	3	0.564
Capnocytophaga	5	4	5	6	0.655

the mucous membrane thickness in the facial marginal region and the facial papilla. After just 4 weeks, there was a significant reduction of the HI from 1.1 to 0.7 ($P = 0.009$), which could predominantly be attributed to a decrease of the papillary thickness of an average 2.9 mm (minimum 1.8 mm, maximum 4.7 mm) to 2.5 mm (minimum 1.4 mm, maximum 4.3 mm). After 8 weeks, the changes were significant both on the papilla (2.2 mm, $P = 0.011$) as well as in the marginal area (baseline: 1.6 mm, 8 weeks: 1.3 mm, $P = 0.021$). With the HI, a significant reduction to 0.4 was also recorded ($P = 0.008$). In the course of the investigation, there were no other significant reductions of the gingival enlargement and gingival width. After 26 weeks, the thickness of the marginal gingiva started to increase again, although the HI and GWP remained unchanged. Effects of local inflammation could be ruled out as PI and GI had remained stable throughout the entire period. Eger et al[20] found a high validity for the thickness measurement with the SDM device. Their results for the facial GWM with periodontally healthy patients varied between 0.8 mm and 1.52 mm. The type of tooth and age of patient was determined to be a factor in the present study. The largest thickness was found on the two mandibular molars.

The effect of plaque-induced gingivitis on the prevalence and degree of gingival enlargement has been described several times[2,8,24]. However, it has also been shown that consequent plaque control cannot prevent the development of gingival changes in every case[25]. In the present study, the PI remained unchanged throughout the entire period, so that influences of the biofilm on the improvement of the HI and the GWM and GWP could be ruled out. The PD reduced significantly after the medication was changed, from 4.6 mm to 3.8 mm (see Table 3). This decrease in PD and gingival enlargement reduces the plaque retention niches, which can promote the growth of strict anaerobes[5]. It was expected that this would be reflected in the present microbiological investigations. Nakou et al[5] examined the composition of the subgingival flora in patients with nifedipine therapy and periodontitis and observed a proliferation-dependent settlement. In the case of patients with gingival enlargement and deeper pockets, larger amounts of fusiform bacteria as well as Capnocytophaga species were found compared with patients without proliferations. Fischer et al[26] reported greater amounts of Gram-negative species and anaerobes in the subgingival microflora of ferrets with ligature-induced periodontitis and ciclosporin A therapy than in ferrets without ciclosporin A therapy[27]. Takada et al[6] reported a significantly larger proportion of obligate Gram-negative anaerobes, such as *P. i.*, in patients with phenytoin-induced gingival enlargement, than in patients without enlargement and in healthy probands. On the other hand, Leung et al[28] found no correlation between the occurrence of gingival enlargement and the quantity and quality of microorganisms. They examined kidney-transplanted patients with ciclosporin A therapy and differentiated between periodontally healthy transplanted patients and transplant recipients with chronic periodontitis. In doing this, they determined that the subgingival microflora of the periodontitis patients, irrespective of the prevalence of the gingival proliferations, contained Gram-negative species and *Borrelia*, and the isolation frequency of fusiform species was significantly higher than in the group of transplanted patients without periodontitis.

It is possible that the pocket created by periodontitis is of greater significance than the niche arising from the enlargement. Romito et al[29] investigated heart transplant patients with and without gingival enlargement during ciclosporin treatment. They found no Gram-negative species in either group, in either saliva or pockets.

In addition, effects of the relevant immunosuppressive medication on the subgingival flora are also conceivable. Pistorius et al[30] described an inhibiting effect on the oral microflora through treatment with ciclosporin A and to a lower degree also with tacrolimus. The microbial changes when switching treatment from ciclosporin A to tacrolimus has not been investigated to date. In the present study, a rather limited effect of the medication change-over on the subgingival microflora was evident. Despite significant reduction of the gingival enlargement, there were only slight changes in the bacterial quanitities for *A.a.*, *E c.*, *P.g.*, *F.n.*, *P.i.*, *T.d.* and Capnocytophaga. The number of patients with high BCS for *T.f.* reduced from seven to two, which could be explained as an indirect effect of the change in medication on the bacterial settlement of the pockets through the reduction of gingival enlargement.

Socransky and Haffajee[31] showed that a direct dependency on the pocket depth exists with the settlement of red complex, to which *T. f.* also belongs. In deep pockets, significantly higher numbers of red complex bacteria were found. This relationship was clearer than with the other bacteria complexes.

Detailed studies of changes in individual bacteria types caused by the change in medication with gingival enlargement, as shown here, are not currently available in the literature.

■ Conclusions

The change from ciclosporin A to tacrolimus led to a significant reduction in gingival enlargement without further impact on the biofilm. These changes occur just 8 weeks after the change in medication and, therefore, represent a clearly noticeable improvement for the patients. The decrease in the gingival thickness leads to positive changes of the subgingival microflora. The number of patients with a high proportion of *T.f.*, associated as the representative of the red complex with destructive processes, is significantly reduced. In the case of patients with ciclosporin A medication and distinct gingival enlargement, changing the immunosuppressant to tacrolimus can be recommended from a periodontal point of view.

■ Acknowledgements

We thank Dr R Schwarz (formerly of the Centre for Surgery, University of Leipzig, Germany) for assigning patients, and Fujisawa Deutschland, Munich, Germany, for supporting the project.

■ References

1. Rateitschak-Plüss EM, Hefti A, Lörtscher R, Thiel G. Initial observation that cyclosporin A induces gingival enlargement in man. J Clin Periodontol 1983;10:237-246.
2. Hallmon WW, Rossmann JA. The role of drugs in the pathogenesis of gingival overgrowth. Periodontol 2000 1999; 21:176-196.
3. Boltchi FE, Rees TD, Iacopino AM. Cyclosporine A-induced gingival overgrowth: A comprehensive review. Quintessence Int 1999;30:775-783.
4. Dannewitz B. Wenn die Gingiva ins Kraut schießt – Ursachen, Risikofaktoren und Therapieoptionen für Gingivawucherungen. Parodontologie 2006;17:307-316.
5. Nakou M, Kamma JJ, Andronikaki A, Mitsis F. Subgingival microflora associated with nifedipin-induced gingival overgrowth. J Periodontol 1998;69:664-669.
6. Takada K, Sugiyama H, Umezawa K, Mega J, Hirasawa M. The subgingival microflora in phenytoin-induced gingival hyperplasia. J Periodont Res 2003;38:477-481.
7. King GN, Fullinfaw R, Higgins TJ, Walker RG, Francis DMA, Wiesenfeld D. Gingival hyperplasia in renal allograft recipients receiving cyclosporin A and calcium antagonists. J Clin Periodontol 1993;20:286-293.
8. Thomason JM, Seymour RA, Rice N. The prevalence and severity of cyclosporin- and nifedipine-induced overgrowth. J Clin Periodontol 1993;20:37-40.
9. Thomason JM, Kelly PJ, Seymour RA. The distribution of gingival overgrowth in organ transplant patients. J Clin Periodontol 1996;23:367-371.
10. Seymour RA, Thomason JM, Ellis JS. The pathogenesis of drug-induced gingival overgrowth. J Clin Periodontol 1996;23:165-175.
11. Seymour RA, Ellis JS, Thomason JM. Risk factors for drug-induced gingival overgrowth. J Clin Periodontol 2000;27: 217-223.
12. Bader G, Lejeune S, Messner M. Reduction of cyclosporin-induced gingival overgrowth following a change to tacrolimus. A case history involving a liver transplant patient. J Periodontol 1998;69:729-732.
13. Kliem V, Brunkhorst R. Tacrolimus in kidney transplantation. Nephron 1998;79:8-20.
14. Wondimu B, Nemeth A, Modeer T. Oral health in liver transplant children administered cyclosporin A or tacrolimus. Int J Paediatr Dent 2001;11:424-429.
15. James JA, Boomer S, Maxwell AP, Hull PS, Short CD, Campbell BA et al. Reduction in gingival overgrowth associated with conversion from cyclosporin A to tacrolimus. J Clin Periodontol 2000;27:144-148.
16. Hernández G, Arriba L, Lucas M, de Andrés A. Reduction of severe gingival overgrowth in a kidney transplant patient by replacing cyclosporin A with tacrolimus. Periodontol 2000; 71:1630-1636.
17. James JA, Jamal S, Hull PS, Macfarlane TV, Campbell BA, Johnson RV, Short CD. Tacrolimus is not associated with gingival overgrowth in renal transplant patients. J Clin Periodontol 2001;28:848-852.
18. Busque S, Demers P, St.-Louis G, Boily JG, Tousignant J, Lemieux F et al. Conversion from neoral (cyclosporine) to tacrolimus of kidney transplant recipients for gingival hyperplasia or hypertrichosis. Transplant Proc 1998;30:1247-1248.
19. Kohnle M, Lütges P, Witzke O, Philipp T, Heemann U. Conversion to tacrolimus in cyclosporin A treated patients with gum hyperplasia. Transplant Proc 1998;30:2122-2123.
20. Eger T, Müller HP, Heinecke A. Ultrasonic determination of gingival thickness. J Clin Periodontol 1996;23:839-845.
21. Silness J, Löe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal conditions. Acta Odontol Scand 1964;24:747-759.
22. Löe H. The gingival index, the plaque index and the retention index systems. J Periodontol 1967;38:610-616.
23. Mutschelknauss R. Untersuchungen über Rezidive bei Gingivahyperplasien. Dtsch Zahnärztbl 1966;20:380.
24. Kantarci A, Cebeci I, Tuncer Ö, Carin M, Firatli E. Clinical effects of periodontal therapy on the severity of cyclosporin A-induced gingival hyperplasia. J Periodontol 1999;70: 587-593.
25. Seymour RA, Smith DG. The effect of plaque control programme on the incidence and severity of cyclosporin-induced gingival changes. J Clin Periodontol 1991;18: 107-110.
26. Fischer RG, Edwardsson S, Klinge B, Attström R. The effect of cyclosporin A on the oral microflora at gingival sulcus of the ferret. J Clin Periodontol 1996,23:853-860.

27. Fischer RG, Edwardsson S, Klinge B. Oral microflora of the ferret at the gingival sulcus and mucosa membrane in relation to ligature-induced periodontitis. Oral Microbiol Immunol 1994;9:40-49.
28. Leung WK, Yau JYY, Lin LJ, Chan AWK, Chu FCS, Tsang CSP et al. Subgingival microbiota of renal transplant recipients. Oral Microbiol Immunol 2003;18:37-44.
29. Romito GA, Lotufo RF, Saraiva L, Pustigiioni AN, Pustigiioni FE, Stolf NA. Superinfecting microorganisms in patients under treatment with cyclosporin-A and its correlation to gingival overgrowth. Pesqui Odontol Bras 2003;17:35-40.
30. Pistorius A, Willershausen B, Callaway A. Effects of selected immunosuppressive drugs on prostaglandin release, protein synthesis and cell proliferation in human gingival fibroblasts and on the growth of plaque bacteria. Eur J Med Res 2003; 8:25-32.
31. Socransky SS, Haffajee AD. Periodontal microbial ecology. Periodontol 2000 2005;38:135-187.

Originally published (in German) in Parodontologie 2007;18:387-395.