Oral Diseases (2006) 12, 309–314. doi:10.1111/j.1601-0825.2005.01200.x

http://www.blackwellmunksgaard.com

ORIGINAL ARTICLE

Oral health in renal transplant recipients administered cyclosporin A or tacrolimus

LC Spolidorio[1], DMP Spolidorio[1], EMS Massucato[2], KH Neppelenbroek[3], NH Campanha[4], MH Sanches[3]

Departments of [1]Physiology and Pathology and [2]Diagnostic and Surgery and [3]Dental Materials and Prosthodontics, Araraquara Dental School, São Paulo State University; [4]Department of Head and Neck Surgery, Heliopolis Hospital, São Paulo, Brazil

OBJECTIVE: The aim of this study was to determine the oral status of renal transplant recipients receiving cyclosporin A (CsA) or tacrolimus (FK-506) as immunosuppressant.

SUBJECTS AND METHODS: A total of 88 renal transplant recipients receiving CsA (63 men and 25 women, mean age 51.4 years) and 67 receiving FK-506 (57 men and 10 women, mean age 33.5 years) were included in the study. Donor type, histocompatibility, cold ischemia time and prior delayed graft function were similar between the two groups. Demographics and pharmacological data were recorded for all subjects.

RESULTS: The results demonstrated that CsA caused a greater number of oral diseases. A greater number of gingival overgrowth was present in patients treated with CsA. However, the combined use with calcium channel blockers increased the gingival overgrowth number. The occurrence of candida in saliva was observed in 80 renal recipients treated with CsA and 20 treated with FK-506. The presence of squamous oral carcinoma ($n = 3$) and herpes simplex ($n = 10$) was observed in patients treated with CsA. These alterations were not observed in renal recipients treated with FK-506.

CONCLUSIONS: Renal recipients constitute a high-risk group for oral diseases, as they are immunocompromised. However, the FK-506 regime appears to ameliorate this effect, compared with CsA. Adequate pre- and post-transplant oral health care is recommended for these subjects, irrespective of the time interval for which the drug is administered.

Oral Diseases (2006) **12**, 309–314

Keywords: oral health; renal transplant; cyclosporin; tacrolimus

Correspondence: Prof. Dr Luís Carlos Spolidorio, Faculdade de Odontologia de Araraquara – UNESP, Rua Humaitá, 1680 Araraquara, São Paulo, CEP 14801-903, Brazil. Tel: +55 016 33016480, Fax: +55 016 33016488, E-mail lcs@foar.unesp.br
Received 25 May 2005; revised 5 July 2005, 27 July 2005; accepted 27 July 2005

Introduction

Tacrolimus (FK-506) was introduced as an immunosuppressive agent for use in organ transplants in 1987 and has gradually been gaining popularity (Spencer *et al*, 1997). Since the primary clinical trials performed in orthotopic liver transplantation in 1989, the drug has been used with encouraging results as primary therapy after renal, hepatic, and cardiac transplantation (Liver, 1994; Shapiro *et al*, 1995; Pham *et al*, 1996). Cyclosporin A (CsA) is a hydrophobic cyclic endecapeptide with unsurpassed immunosuppressive activity (Feldman, 2000). It is used for the treatment of several diseases such as rheumatoid arthritis, psoriasis, nephrotic syndrome, and inflammatory bowel disease, and to prevent organ rejection in transplantation (Feldman, 2000). Studies of the biological mechanisms of CsA have shown that the drug, cyclophilin complex, binds and inhibits calcineurin, a calcium and calmodulin-dependent serine threonine phosphatase (Shin *et al*, 1997). This inactivation prevents dephosphorylation of nuclear factor of activated T cells (NF-AT), the nuclear import of NF-AT, and the formation of a transcriptionally active NF-AT complex. The net consequence, inhibition of interleukin-2 (IL-2) gene expression at the transcriptional level, is considered to be the primary mechanism for the immunosuppressive activity of CsA. (Ellis and Avner, 1986). The pharmacodynamics of FK-506 is very similar to CsA (Spencer *et al*, 1997). FK-506 binds with FK-binding proteins to form a complex, in a way similar to which CsA binds to cyclophilins. 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 *et al*, 1993). As with CsA, type 1 T-helper cells are suppressed preferentially to type 2 helper cells, and T-cell-mediated toxicity is impaired (Thomson *et al*, 1995). FK-506 has an immunosuppressive capacity 100 times that of

CsA (Jacobson *et al*, 1998), and is recognized as an effective alternative to CsA in primary and rescue therapy. In primary therapy it has been suggested that it may be more effective than CsA in preventing acute and chronic rejection of liver transplants (Spencer *et al*, 1997). FK-506 shares many unwanted effects common to other immunosuppressive agents. It demonstrates an increased tendency for renal recipients to develop diabetes and neurotoxicity when compared with CsA (Mueller *et al*, 1994; Marchetti and Navalesi, 2000), and similar levels of nephrotoxicity (Porayko *et al*, 1994). In contrast, hyperlipidemia, hypertension, and hirsutism are less likely with FK-506 than CsA (Mihatsch *et al*, 1998). The clinical use of CsA is associated with adverse side effects including nephrotoxicity, hepatotoxiciy, hypertension, neurotoxicity, and hypertricosis In the mouth, the main side effect is gingival overgrowth (Rateitschak-Pluss *et al*, 1983). Other oral lesions are poorly described. Numerous case reports suggest that the severity of gingival overgrowth seen in subjects taking FK-506 is lesser than that seen with CsA. The aim of this study was to determine the oral status of renal transplant recipients receiving either CsA or FK-506 as immunosuppressant.

Subjects and methods

Subjects

The present study received ethical approval from the appropriate São Paulo Hospital Ethical Committee (Proc. 1286/03). A total of 155 renal transplant recipients (120 men and 35 women, mean age 42.4 years) were recruited from São Paulo Hospital. All renal transplant recipients were medicated with either CsA or FK-506 alone or together with calcium channel blockers (CCB). Only subjects who possessed a minimum of eight of the ten most anterior teeth in the upper or lower dental arches participated in the study. Demographic variables including age, gender, time since transplant, and pharmacological data were recorded for all subjects. Two clinicians performed oral examinations of all subjects. In the case of mucosa alterations, the histological analysis was performed using hematoxylin and eosin.

Collection of saliva

Saliva was collected from each subject using a spitting method in sterile tube. The tubes with the saliva were submitted to 1 min of vibration in order to obtain a uniform suspension. After this procedure, the saliva was diluted in decimal series from 100^{-1} to 10^{-3} in sterile saline solution. For the cultivation of yeasts, aliquots of 100 μl of each dilution were inoculated in Sabouraud dextrose agar chloramphenicol medium, and incubated at 37°C for 48 h. The counting of colony-forming units ml^{-1} was carried out after growth of characteristic yeast colonies. *Candida* species were identified by wet preparation of a colony for microscopic examination and by germ-tube testing. The growth characteristics in Sabouraud dextrose broth, morphologic characteristics on cornmeal agar with Tween 80, and the ability of the fungi to grow in the presence of cycloheximide were evaluated. Urease activity testing and carbohydrate assimilation and fermentation tests were performed as required.

Oral hygiene

Oral hygiene status was assessed by the visible plaque index (VPI) (Axelsson and Lindhe, 1975). The presence of dental biofilm was revealed using a disclosing agent. The VPI% was expressed as the number of surfaces exhibiting visible biofilm divided by the total number of surfaces available. Gingival inflammation was estimated according to the gingival bleeding index (GBI). The frequency of surfaces with gingivitis for each patient (GBI%) was based on the occurrence of bleeding on probing the gingival sulcus at six points around each tooth (Axelsson and Lindhe, 1975; Wondimu *et al*, 2001).

Gingival examination

Gingival overgrowth was determined on the basis of measurements of sulcus depth and diagnosed as positive when the probing depth (PD) $>= 4$ mm without exhibiting loss of periodontal attachment, i.e., pseudopockets (Wondimu *et al*, 1993, 2001). Sulcus PD was measured to the nearest millimeter at four points around each tooth using a graded periodontal probe. The level of periodontal attachment of the sites exhibiting a PD $>= 4$ mm, was assessed from radiographs taken by a paralleling technique. Loss of attachment was diagnosed when the distance between the cemento-enamel junction and marginal bone on the radiographs exceeded 2 mm. Gingival overgrowth was diagnosed as positive when the patient exhibited one or more pseudopockets of PD $>= 4$ mm.

Statistical analysis

Individual subject data, including demographic, pharmacological, periodontal and oral mucosa variables, were collected and transcribed onto a statistical database (Minitab 2000, USA). The Mann–Whitney *U*-test and Fisher's exact test were used to test for statistical differences found ($\alpha = 0.05$).

Results

A total of 155 renal allograft recipients medicated with FK-506 ($n = 67$) or CsA ($n = 88$) participated in the study. Before renal transplantation subjects presented with either diabetes or hypertension. However, the renal allograft recipients treated with FK-506 presented neurotoxicity ($n = 6$), diabetes ($n = 2$) and hypertension ($n = 6$), while most of the renal allograft recipients treated with CsA presented hypertension ($n = 64$) and hypertricosis ($n = 33$). The FK-506 group was younger (33.5 ± 7.8 years) than the CsA group (51.4 ± 5.9 years). In all cases most of the renal transplant recipients were men. The mean dosage of CsA was 10 mg kg^{-1} of body weight day^{-1} and that of FK-506 1.0 mg kg^{-1} of body weight day^{-1} (Table 1).

All renal allograft recipients with hypertension were treated with CCB.

The mean age of the renal transplant recipients treated with FK-506 alone was younger (31.8 ± 4.1 years), whereas those treated with CsA alone was 57.6 ± 3.2 years The time since transplant varied between 4.6 and 4.8 years. The demographic and pharmacological data for the FK-506 and CsA subjects, dichotomized into those taking CCB, are presented in Table 2. Overall, six renal allograft recipients were medicated with FK-506 and CCB (six men) and 64 were medicated with CsA and CCB (60 men and four women). In most of the cases the subjects were men and the time since transplant varied between 1 and 7 years (Table 2).

Gingival overgrowth characterized by one or more units with increased sulcus PD (PD > = 4 mm), was found in 54 renal recipients treated with CsA and CCB, and 14 treated with CsA alone ($P < 0.05$). In contrast to the CsA group, the group treated with FK-506 alone did not present gingival overgrowth ($n = 0$), and when the treatment was associated with CCB, gingival overgrowth was observed in six renal recipients ($P < 0.05$) (Table 3).

The level of oral hygiene was good in all renal allograft recipients and there was no difference between the groups. One hundred renal allograft recipients of the 155 renal transplanted recipients presented candida in the saliva. *Candida albicans* was the most frequent species identified in the groups treated with CsA ($n = 66$) or FK-506 ($n = 17$). Besides *C. albicans* only *Candida dubliniensis* ($n = 3$) was observed in the saliva of recipients treated with FK-506. On the other hand, the renal transplanted recipients treated with CsA presented *C. dubliniensis* ($n = 10$), *Candida parapsilosis* ($n = 2$), *Candida krusei* ($n = 1$), and *Candida tropicalis* ($n = 1$) (Table 4). Only the CsA group presented squamous cell carcinoma of the lip ($n = 3$) and herpes simplex ($n = 10$) (Table 5).

Table 1 Demographic, drug variable and systemic alterations of the renal recipients treated with FK-506 or CsA

Variables	*CsA (n = 88)*	*FK-506 (n = 67)*
Age (years), mean ± SD	51.4 ± 5.9[a]	33.5 ± 7.8
Gender (m/f)	63/25	57/10
Dosage (mg)	10.0 ± 10.0	1.0 ± 0.5
Neurotoxicity	0	6
Diabetic	0	2
Hypertension	64[a]	6
Hypertricosis	33	0

Values are expressed in *n*. CsA, cyclosporin A; FK-506, tacrolimus.
[a]Significant difference from FK-506.

Discussion

The introduction of CsA in the 1980s marked a significant clinical advance in the treatment of organ transplant recipients (Starzl *et al*, 1986; Gjertson, 1991; Gjertson *et al*, 1995). The use and the systemic effects of this drug have been studied. In more recent years, new drugs, including CsA microemulsion, FK-506 and mycophenolate mofetil, have added to the growing success of organ transplantation. Concomitant with this success, however, there is need for special care in the selection of immunosuppressive regimens. The selection of appropriate immunosuppressive regimen is individualized and based on a clear understanding of clinical efficacy and associated risks and/or long-term complications (Henry, 1999). As such, it is of interest to consider oral health. In terms of safety, the principal toxicities of FK-506 appear to be neurologic complications, gastrointestinal disturbances, and increased diabetogenicity. Toxicities associated with CsA administration are hypercholesterolemia and, in some cases, hypertension (Henry, 1999). In the present study, the renal allograft recipients treated with FK-506 presented neurotoxicity ($n = 6$), diabetes ($n = 2$) and hypertension ($n = 6$). The majority of recipients treated with CsA presented hypertension ($n = 64$) and hypertricosis ($n = 33$). All subjects who participated in the present study did not present diabetes or hypertension before renal transplantation. There is, however, a lack of information comparing the effects of these drugs on oral health, and most of the studies available have investigated the incidence of CsA-induced gingival overgrowth. Therefore, the aim of this study was to determine the oral status of renal allograft recipients receiving either CsA or FK-506 as immunosuppressant. The mean age of the renal transplant recipients receiving FK-506 was, in general, lower than that of subjects treated with CsA. These data are in agreement with previous findings (McKaig *et al*, 2002). Over the past few years, FK-506 has gained wider acceptance as a first-line immunosuppressant therapy for renal

Table 2 Variables analyzed in the renal transplant recipients treated with FK-506 or CsA alone or in association with CCB

Variables	*CsA (n = 24)*	*CsA and CCB (n = 64)*	*FK-506 (n = 61)*	*FK-506 and CCB (n = 06)*
Age (years), mean ± SD (range)	57.6 ± 3.2[a] (48–65)	44.4 ± 2.84 (42–47)	31.8 ± 4.1(28–36)	35.1 ± 10.7 (32 – 39)
Gender (m/f)	17/7	60/4	41/20	6/0
Time since transplant (years)	4.6 ± 3.5 (1–7)	5.8 ± 3.5 (1–7)	4.8 ± 2.6 (1–5)	3.4 ± 2.8 (1–6)

Values are expressed in *n*. CsA, cyclosporin A; CCB, calcium channel blocker; FK-506, tacrolimus.
[a]Significant difference from FK-506.

Table 3 Gingival overgrowth of renal transplanted recipients treated with CsA alone, FK-506 alone or a combination of CsA and CCB, or FK-506 and CCB

Variables	*Gingival overgrowth (n = 94) (%)*
FK-506	0/6
FK-506 + CCB	6/6[a] (100)
CsA	14/24 (58.3)
CsA + CCB	54/64[b] (84.3)

Values are expressed in *n*. CsA, cyclosporin A; CCB, calcium channel blocker; FK-506, tacrolimus.
[a]Significant difference from FK-506.
[b]Significant difference from CsA.

Table 4 Frequency of oral candidal colonization in renal transplant subjects

Organism	*CsA*	*FK-506*
C. albicans	66	17[a]
C. dubliniensis	10	03
C. parapsilosis	02	–
C. krusei	01	–
C. tropicalis	01	–

Values are expressed in *n*. CsA, cyclosporin A; FK-506, tacrolimus.
[a]Significant difference from CsA.

Table 5 Oral lesions of renal transplant recipients treated with CsA alone, FK-506 alone or a combination of CsA and CCB, or FK-506 and CCB

Variables	*Squamous oral carcinoma*	*Herpes simplex*
CsA	3	10
CsA and CCB	–	–
FK-506	–	–
FK-506 and CCB	–	–

Values are expressed in *n*. CsA, cyclosporin A; CCB, calcium channel blocker; FK-506, tacrolimus.

transplantation. As a consequence of this and of renal transplantation being performed in young individuals, the mean age of renal allograft recipients in the FK-506 group was lower.

The findings of the present study demonstrate that renal allograft recipients who have been under a CsA-based immunosuppressive regimen presented gingival overgrowth, an increased incidence of *Candida* sp. in the saliva, squamous oral carcinoma and herpes simplex. The renal allograft recipients treated with FK-506 also presented gingival overgrowth and *Candida* sp. in the saliva, however the incidence was lower ($P > 0.05$).

Gingival overgrowth was diagnosed as positive when the patient exhibited one or more units of increased sulcus ($PD >= 4$ mm) without loss of periodontal attachment. The relationship between gingival overgrowth and CsA therapy is well documented in humans and experimental animals, and there is a consensus that FK-506 causes less overgrowth, and when it occurs it is less severe (Ellis *et al*, 2004). The concomitant medication with CCB increased the presence of gingival alterations in renal transplant recipients medicated with CsA. Morisaki *et al* (2000) suggested that renal allograft recipients who were treated concurrently with CCB, more specifically nifedipine, presented more severe gingival overgrowth than those who were treated with CsA alone. On the other hand no gingival overgrowth was observed in patients treated with FK-506 alone. These results clearly demonstrate that the CCB therapy presented an increase in the risk of development of gingival alterations in patients treated with FK-506. The majority of the renal recipients analyzed in the present study were treated with nifedipine. Nifedipine is a well-known CCB, and CsA, like FK-506, seems to act via calcium (Ferraris *et al*, 2004). The common mechanism for the effects of CsA and CCB appears to be Ca^{2+} mobilization. Several other factors are associated with the induction of gingival overgrowth. As commented by Kataoka *et al* (2000), genetic predisposition, gender, age, dose and duration of CsA are involved in the pathogenesis of drug-induced gingival overgrowth. Some studies have suggested that the dental biofilm can probably modify the characteristics of the overgrowth, but is not essential for its development (Seymour and Smith, 1991; Somacarrera *et al*, 1994; Ellis *et al*, 2004). In fact, the relationship between gingival inflammation and the development of gingival overgrowth is still unclear, although a positive correlation has been suggested (Seymour *et al*, 2000). In the present study, the dental biofilm was assessed and, in general, the patients demonstrated good oral hygiene with no clinical signs of inflammatory gingival disease. The results showed that gingival inflammation seemed not to be involved in the pathogenesis of drug-induced gingival overgrowth. Nevertheless, the molecular mechanisms that are involved in the accumulation of collagen in the gingiva are not yet well understood.

Despite advances in immunosuppressive regimens over the past decade, infectious complications after kidney transplantation remain an important cause of morbidity and mortality (Hwang *et al*, 2004). In the present work fungal species were the most frequent organism, followed by herpes simplex.

The present study showed the incidence of *Candida* sp. in saliva of patients treated with CsA or FK-506. Some works described candida-induced lesions. Angular cheilitis has been described in up to 4% of renal allograft recipients (King *et al*, 1994; Klassen and Krasko, 2002). Other oral candidal lesions – such as pseudomembranous (1.9%), erythematous (3.8%), and chronic atrophic candidosis (3.8%) – have been reported in renal allograft recipients (King *et al*, 1994). These findings suggest that the prevalence as well as the interrelationship between various species of *Candida* inhabiting the human cavity may be clinically important factors in renal transplant recipients. It is interesting to point out that the renal allograft recipients treated with CsA presented larger *Candida* sp. in the saliva – a fact undocumented in the literature. Some studies have

shown that transplanted subjects treated with CsA present xerostomia (Tyrzyk *et al*, 2004; Diaz-Ortiz *et al*, 2005). Xerostomia is a condition that induces a greater incidence of *Candida* sp. (Torres *et al*, 2003). The lower saliva flow rates induced changes in oral soft tissues and an increase in the number of oral *Candida* sp. (Tyrzyk *et al*, 2004). In the present study, the saliva flow rates were not evaluated. Herpes simplex infection (HSV) was detected in 10 renal allograft recipients treated with CsA alone. No HSV was observed in the renal allograft recipients treated with FK-506. Recent findings suggest that viral infection has always been a major threat to kidney transplant subjects on immunosuppressive therapy (Hwang *et al*, 2004). These results are not in accordance with the findings of the present work. Perhaps the results of the present work can be explained by the use of effective anti-herpetic regimens (Squifflet and Legendre, 2002). These authors verified that most of the patients that presented with HSV were treated with CsA. This finding is in line with the present work. In the present study anti regimens were not evaluated.

In the present investigation, three cases of squamous oral carcinoma of the lip in CsA-treated renal recipients were also observed. Some reports suggest that therapy following renal transplantation predisposes to epithelial dysplasia and carcinoma of the lip (Regev *et al*, 1992; Thomas *et al*, 1993). Previous studies indicated that CsA-treated recipients are more susceptible to the development of malignancies such as lymphoma (Nalesnik *et al*, 2000; Gardner *et al*, 2004; Sinha *et al*, 2004), Kaposi's sarcoma (Campistol *et al*, 2004; Moosa, 2005), cervix carcinoma (Goldfarb *et al*, 1997), and solitary plasmocytoma (Yoon *et al*, 2003). There have been reports of squaomous oral carcinoma and Kaposi's sarcoma arising within areas of CsA-induced gingival overgrowth (Vargas and Tyldesley, 1991; Quinibi *et al*, 1998). In the present study no clinically malignant alterations in gingival overgrowth were observed. The incidence of squaomous oral carcinoma and basal cell carcinoma is notably increased after organ transplantation (Hyckel *et al*, 2003). However, the majority of reports regarding carcinoma associated with immunosuppression are related to the skin. The incidence of skin carcinoma rises progressively with the duration of graft survival from an accumulative risk of 10% after 10 years to a risk of 40% 20 years after graft survival. In the present study the majority of renal recipients that presented oral carcinoma had undergone treatment for 1–7 years.

In summary, the present study investigated a group of renal allograft recipients, and demonstrated a greater incidence of oral lesions in the patients on a CsA-based immunosuppressive regimen than in the patients on a FK-506-based immunosuppressive regimen. Renal transplant recipients constituted a high-risk group for oral diseases, due to that fact that they are immunocompromised. However, the FK-506 regimen appeared to ameliorate this effect, compared with CsA. Adequate pre- and post-transplant oral health care is recommended for these subjects, irrespective of the time interval for which the drug is administered.

References

Axelsson P, Lindhe J (1975). Effect of fluoride on gingivitis and dental caries in a preventive program based on plaque control. *Community Dent Oral Epidemiol* **3:** 156–160.

Campistol JM, Gutierrez-Dalmau A, Torregrosa JV (2004). Conversion to sirolimus: a successful treatment for post transplantation Kaposi's sarcoma. *Transplantation* **77:** 760–762.

Diaz-Ortiz ML, Mico-Llorens JM, Gargallo-Albiol J *et al* (2005). Dental health in liver transplant patients. *Med Oral Patol Oral Cir Bucal* **10:** 66–72.

Ellis D, Avner ED (1986). Renal failure and dialysis therapy in children with hepatic failure in the perioperative period of orthotopic liver transplantation. *Clin Nephrol* **25:** 295–303.

Ellis JS, Seymour RA, Taylor JJ *et al* (2004). Prevalence of gingival overgrowth in transplant patients immunosuppressed with tacrolimus. *J Clin Periodontol* **31:** 126–131.

Feldman S. (2000). Advances in psoriasis treatment. *Dermatol Online J* **6:** 4.

Ferraris JR, Tambutti ML, Cardoni RL *et al* (2004). Conversion from cyclosporine A to tacrolimus in pediatric kidney transplant recipients with chronic rejection: changes in the immune responses. *Transplantation* **77:** 532–537.

Fruman DA, Klee CB, Bierer BE *et al* (1992). Calcineurin phosphatase activity in T-lymphocytes is inhibited by FK-506 and cyclosporin A. *Proc Natl Acad Sci USA* **89:** 3686–3690.

Gardner RV, Velez MC, Ode DL *et al* (2004). Gamma/delta T-cell lymphoma as a recurrent complication after transplantation. *Leuk Lymphoma* **45:** 2355–2359.

Gjertson DW (1991). Survival trends in long-term first cadaver-donor kidney transplants. *Clin Transpl* **8:** 225–235.

Gjertson DW, Cecka JM, Terasaki PI (1995). The relative effects of FK506 and cyclosporine on short- and long-term kidney graft survival. *Transplantation* **60:** 1384–1388.

Goldfarb DA, Neumann HP, Penn I (1997). Results of renal transplantation in patients with renal cell carcinoma and von Hippel-Lindau disease. *Transplantation* **64:** 1726–1729.

Henry ML (1999). Cyclosporine and tacrolimus (FK506) – a comparison of efficacy and safety profiles. *Clin Transplant* **13:** 209–220.

Hwang EA, Kang MJ, Han SY, Park SB, Kim HC (2004). Viral infection following kidney transplantation: long-term follow-up in a single center. *Transplant Proc* **36:** 2118–2119.

Hyckel P, Schleier P, Meerbach A (2003). The therapy of virus-associated epithelial tumors of the face and the lips in organ transplant recipients. *Med Microbiol Immunol* **192:** 171–176.

Jacobson P, Uberti J, Ratanatharathon V (1998). Tacrolimus: a new agent for the prevention of graft-versus-host disease in hematopoietic stem cell transplantation. *Bone Marrow Transplant* **22:** 217–225.

Kataoka M, Shimizu Y, Kunikio K *et al* (2000). Cyclosporin A decreases the degradation of type I collagen in rat gingival overgrowth. *J Cell Physiol* **182:** 351–358.

King GN, Healy CM, Glover MT *et al* (1994). Prevalence and risk factors associated with leukoplakia, hairy leukoplakia, erythematous candidosis and gingival hyperplasia in renal transplant recipients. *Oral Surg Oral Med Oral Pathol* **78:** 718–726.

Klassen JT, Krasko BM (2002). The dental health status of dialysis patients. *J Can Dent Assoc* **68:** 34–38.

Liver EF (1994). European FK506 Multicentre Liver Study Group, Randomised trial comparing tacrolimus (FK-506) and cyclosporin in prevention of liver allograft rejection. *Lancet* **334:** 423–428.

Marchetti P, Navalesi R (2000). The metabolic effects of cyclosporin and tacrolimus. *J Endocrinol Invest* **23:** 482–490.

McKaig SJ, Kelly D, Shaw L (2002). Investigation of the effect of FK506 (tacrolimus) and cyclosporin on gingival overgrowth following paediatric liver transplantation. *Int J Paediatr Dent* **12:** 398–403.

Mihatsch MJ, Kyo M, Morozumi K *et al* (1998). The side-effects of cyclosporine-A and tacrolimus. *Clin Nephrol* **49:** 356–363.

Moosa MR (2005). Racial and ethnic variations in incidence and pattern of malignancies after kidney transplantation. *Medicine* **84:** 12–22.

Morisaki I, Fukui N, Fujimori Y *et al* (2000). Effects of combined oral treatments with cyclosporine A and nifedipine or diltiazem on drug-induced gingival overgrowth in rats. *J Periodontol* **71:** 438–443.

Mueller AR, Platz KP, Bechstein WO (1994). Neurotoxicity after orthoptic liver transplantation. A comparison between cyclosporine and FK-506. *Transplantation* **58:** 155–170.

Nalesnik M, Jaffe R, Reyes J *et al* (2000). Posttransplant lymphoproliferative disorders in small bowel allograft recipients. *Transplant Proc* **32:** 1213.

Pham SM, Kormos RL, Hattler BG *et al* (1996). A prospective trial of tacrolimus (FK-506) in clinical transplantation: intermediate-term results. *J Thorac Cardiovasc Surg* **111:** 764–772.

Porayko DA, Klee CB, Bierer BE *et al* (1994). Calcineurin phosphatase activity in T-lymphocytes is inhibited by FK-506 and cyclosporin A. *Proc Natl Acad Sci USA* **89:** 3686–3690.

Quinibi W, Al-Furayh O, Almeshari *et al*. (1998). Serologic association of human herpesvirus eight with posttransplant Kaposi's Sarcoma in Saudi Arabia. *Transplantation* **27**, 583–585.

Rateitschak-Pluss EM, Hefti A, Lortscher R *et al* (1983). Initial observation that cyclosporin-A induces gingival enlargement in man. *J Clin Periodontol* **10:** 237–246.

Regev E, Zeltser R, Lustmann J (1992). Lip carcinoma in renal allograft recipient with long-term immunosuppressive therapy. *Oral Surg Oral Med Oral Pathol* **73:** 412–414.

Seymour RA, Smith DG (1991). The effect of a plaque control programme on the incidence and severity of cyclosporin-induced gingival changes. *J Clin Periodontol* **18:** 107–110.

Seymour RA, Ellis JS, Thomason JM (2000). Risk factors for drug-induced gingival overgrowth. *J Clin Periodontol* **27:** 217–223.

Shapiro R, Jordan ML, Scantlebry VP *et al* (1995). A prospective randomized trial of FK-506-based immunosuppression after renal transplantation. *Transplantation* **59:** 485–490.

Shin GT, Khanna A, Sharma VK *et al* (1997). In vivo hyperexpression of transforming growth factor-beta 1 in humans: stimulation by cyclosporine. *Transplant Proc* **29:** 284.

Sinha A, Velangi S, Natarajan S (2004). Non-Hodgkin's lymphoma following treatment of atopic eczema with cyclosporin A. *Acta Derm Venereol* **84:** 327–328.

Somacarrera ML, Hernandez G, Acero J *et al* (1994). Factors related to the incidence and severity of cyclosporin-induced gingival overgrowth in transplant patients. A longitudinal study. *J Periodontol* **65:** 671–675.

Spencer CM, Goa KL, Gilliis JC (1997). Tacrolimus. An update its pharmacology and clinical efficacy in the management of organ transplantation. *Drugs* **54:** 925–975.

Squifflet JP, Legendre C (2002). The economic value of valacycloviv prophylaxis in transplantation. *J Infect Dis* **186** (Suppl. 1)**:** S116–S122.

Starzl TE, Iwatsuki S, Shaw BW Jr *et al* (1986). Liver transplantation in the ciclosporin era. *Prog Allergy* **38:** 366–394.

Thomas DW, Seddon SV, Shepherd JP (1993). Systemic immunosuppression and oral malignancy: a report of a case and review of the literature. *Br J Oral Maxillofac Surg* **31**, 391–393.

Thomson AW, Bonham CA, Zeevi A (1995). Mode of action of tacrolimus (FK-506): molecular and cellular mechanisms. *Ther Drug Monit* **17:** 584–591.

Torres SR, Peixoto CB, Caldas DM *et al* (2003). Clinical aspects of *Candida* species carriage in saliva of xerotomic subjects. *Med Mycol* **41:** 411–415.

Tyrzyk S, Sadlak-Nowicka J, Kedzia A *et al* (2004). Clinical and mycological examinations of oral mucosa in cyclosporine A treated patients after renal transplantation. *Przegl Lek* **61:** 467–472.

Vargas E, Tyldesley WR (1991). Carcinoma arising in cyclosporin-induced gingival hyperplasia. *Br Dent* **6**, 26–27.

Wiederrecht G, Lam, E, Hung S *et al* (1993). The mechanism of action of FK-506 and cyclosporin A. *Ann N Y Acad Sci* **696:** 9–19.

Wondimu B, Dahllof G, Berg U *et al* (1993). Cyclosporin-A-induced gingival overgrowth in renal transplant children. *Scand J Dent Res* **101:** 282–286.

Wondimu B, Németh A, Modéer T (2001). Oral health in liver transplant children administered cyclosporin A or tacrolimus. *Int J Paediatr Dent* **11:** 424–429.

Yoon JH, Yook JI, Kim HJ, Cha IH, Yang WI, Kim J (2003). Solitary plasmacytoma of the mandible in a renal transplant recipient. *Int J Oral Maxillofac Surg* **32:** 664–666.