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Regression of Cyclosporine A-Induced Gingival Hyperplasia Following Switch to Tacrolimus in Renal Transplant Recipients

Regresja przerostu dziąseł po konwersji CsA na tacrolimus u chorych po przeszczepieniu nerki

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Abstract

Background and Objectives. Gingival hyperplasia (GH) is a side effect of cyclosporine A treatment. The definite cause of this pathology has not been found yet. The objective of the study was to assess the impact of CsA dosage, CsA trough level, gender of calcium channel blocker and HLA phenotype on GH. Also, the effect on CsA-induced GH of a switch to tacrolimus was evaluated.

Material and Methods. The study carried out in the years 1994–2002 included 162 kidney transplant recipients; 124 patients received CsA and 38 patients tacrolimus.

Results. GH of different degree was found in 46% of patients treated with CsA. GH was CsA dose dependent and was found in half of the patients with HLA-DR2 allele. GH was observed in 47% of patients treated with amlodipine and 35% of patients treated with verapamil. GH was found twice as often in males than in females. Gingival overgrowth was not found in patients treated with tacrolimus. Six patients with second and third degree of GH were converted to tacrolimus therapy. After one year of tacrolimus treatment full regression of GH was found.

Conclusions. This study showed high frequency of GH in renal graft recipients treated with CsA. GH severity was larger in patients treated simultaneously with amlodipine. CsA dosage, male sex and HLA-DR2 phenotype were risk factors of GH. None of the patients treated with tacrolimus, even combined with amlodipine, had GH. Switching CsA therapy to tacrolimus resulted in a regression of GH (*Adv Clin Exp Med* 2005, 14, 1, 69–73).

Key words: renal transplantation, gingival hyperplasia, cyclosporine A, tacrolimus, HLA-DR antigens.

Streszczenie

Wprowadzenie i cel pracy. Przerost dziąseł jest niepożądanym skutkiem ubocznym leczenia cyklosporyną A. Dotychczas nie poznano przyczyny tej patologii. Celem badań była ocena wpływu dawki CsA i stężenia CsA, rodzaju stosowanego blokera kanału wapniowego i fenotypu HLA na występujący przerost dziąseł. Zbadano również wpływ zmiany leku z CsA na tacrolimus na istniejący przerost.

Materiał i metody. Badaniami przeprowadzonymi w latach 1994–2002 objęto 162 pacjentów po przeszczepieniu nerki; 124 z nich było leczonych CsA, 38 otrzymywało tacrolimus jako lek immunosupresyjny.

Wyniki. Stwierdzony klinicznie przerost dziąseł o różnym nasileniu wystąpił u 46% pacjentów leczonych CsA i u połowy pacjentów z fenotypem HLA-DR2. Był zależny od dawki CsA i wystąpił u 47% pacjentów leczonych amlodypiną i 35% leczonych werapamillem. Występował dwa razy częściej u mężczyzn w porównaniu z leczonymi kobietami. Nie stwierdzono przerostu dziąseł u pacjentów leczonych tacrolimusem. U sześciu pacjentów z obecnym przerostem dziąseł drugiego i trzeciego stopnia zastosowano zmianę leku z CsA na tacrolimus. Po roku stwierdzono wycofanie się przerostu dziąseł.

Wnioski. Badania wykazały dużą częstość występowania przerostu dziąseł u chorych po przeszczepieniu nerki leczonych CsA. Nasilenie przerostu było większe u pacjentów leczonych także amlodypiną. Czynniki ryzyka przerostu dziąseł były: dawka CsA, płeć męska i fenotyp HLA-DR2. U żadnego z pacjentów leczonych tacrolimusem, nawet w połączeniu z amlodypiną, nie stwierdzono przerostu. Zmiana stosowanej CsA na tacrolimus spowodowała wycofanie się istniejącego wcześniej przerostu dziąseł (*Adv Clin Exp Med* 2005, 14, 1, 69–73).

Słowa kluczowe: przeszczepienie nerki, przerost dziąseł, cyklosporyna A, tacrolimus, antygeny HLA-DR.

Gingival hyperplasia (GH) is a serious problem in patients who receive maintenance CsA treatment. It is associated not only with unsightly appearance, bleeding, proneness to infections but it also considerably hinders biting and chewing of food, which may lead to various alimentary tract diseases. Also, malignant neoplasms development was observed in overgrown gingivae [1].

Gingival overgrowth is the result of hyperplasia of connective tissue components and gingival epithelium, and it is closely associated with parodontium. Up to now the pathogenic mechanisms of CsA-induced GH have not been thoroughly described. Here follow some of the possible risk factors of gingival overgrowth: non-specific state of gingivae inflammation, low level of oral cavity hygiene, local anatomical conditions as well as genetic factors [2]. The connection between gingival overgrowth, CsA dosage and treatment duration has not been fully explained yet.

Calcium channel blockers belong to the group of drugs causing GH. Nifedipin used together with CsA intensifies GH. Such effect was not found when other blockers were used. Gingival overgrowth changes are observed in 2% of patients from healthy population [3, 4]. The other calcineurin inhibitor, tacrolimus, was not associated with GH [5–7].

The objective of this study was to estimate of degree and extent of CsA-induced GH dependent on CsA dosage and concentration, gender of calcium channel blocker used as well as HLA phenotype. The other purpose was to evaluate the effect of a switch CsA therapy to tacrolimus in patients with CsA-induced GH.

Material and Methods

The study carried out in the years 1994–2002 included 162 kidney transplant recipients. In the treatment, 124 patients received CsA with azathioprine (Aza) or mycophenolate mofetil (MMF) combined with corticosteroids (P) and 38 patients (16 females/22 males, aged 38 ± 11) received tacrolimus with Aza or MMF and P. During the first 3 months patients received 7 to 12 mg/kg CsA and in the maintenance treatment 1.8 to 4 mg/kg CsA. Tacrolimus was given 0.2 mg/kg, and in the maintenance treatment, 0.06–0.1 mg/kg. All of the patients received calcium channel blockers; those treated with CsA, verapamil 120–240 mg daily (80%), the remaining, amlodipine 5–10 mg/24 h.

Degree of GH was assessed on a four-degree scale: 0 – no GH; 1 – faint interdental papilla overgrowth; 2 – marginal gingivae and interdental papilla overgrowth; 3 – marginal gingivae and

interdental papilla overgrowth reaching above half of the teeth crowning. Also, the extensiveness of the GH and the number of the gingival units affected were evaluated and expressed in percentages. The patients were divided into three groups, depending upon GH prevalence: group 1 – GH affecting 100–91% of gingival units; group 2 – GH affecting 90–51% of gingival units; group 3 – third and second degree GH affecting 50–25% of gingival units; group 4 – patients with zero or marginal GH affecting single gingival units.

Six patients with second and third degree of GH were converted to tacrolimus therapy. In the examined groups, trough CsA level and total CsA dosage in the first year after transplantation was assessed. Moreover, the total CsA dosage from the beginning of the treatment till the first dental examination was calculated. Also, the impact of calcium channel blockers (verapamil and amlodipine) which patients received combined with CsA upon GH was analysed.

The study of HLA antigens class II prevalence in all patients after kidney transplantation treated with CsA or tacrolimus, and in patients who suffered and did not suffer from GH. Also, the impact of age, gender and creatinine level on GH was studied. Oral hygiene level was assessed with the use of Löe and Silness Plaque Index (PI) and Calculus Index (CI),

Statistical Analysis

Results are presented as a mean \pm SD. Comparison between two means was analyzed by Student's *t*-test. Spearman Rank Correlations Test were used. $p < 0.05$ was accepted as statistically significant.

Results

46.7% of patients treated with CsA suffered from various degrees of GH. None of the patients treated with tacrolimus suffered from GH. GH of 2nd and 3rd degree was found in 36 patients (29%). GH of the same degree but affecting less than 50% of dental units was found in 22 patients. Clinical characteristic of the examined groups of patients with different degrees and extent of GH are presented in Table 1. GH was present much more often in men than in women. Out of 70 examined men GH was seen in 43 (61%) whereas out of 54 examined women GH was found in 15 patients (27%). No association was seen between the age of patients and GH. CsA trough level in whole blood in the first year after

Table 1. Clinical characteristic of patients treated with CsA with gingival hyperplasia of different degree and patients treated with tacrolimus**Tabela 1.** Charakterystyka kliniczna pacjentów leczonych CsA z przerostem dziąseł różnego stopnia i pacjentów leczonych tacrolimusem

	Group 1 (Grupa 1)	Group 2 (Grupa 2)	Group 3 (Grupa 3)	Group 4 (Grupa 4)	Tacrolimus treated group (Grupa pacjentów leczonych tacrolimusem)
Number of patients (Liczba pacjentów)	19	17	22	66	38
Sex (Płeć)	3 F/16 M	2 F/15 M	10 F/12 M	29 F/37 M	16 F/22 M
Age – years (Wiek – lata)	41 ± 12.9	41 ± 8.9	40.1 ± 11	41 ± 12.9	38 ± 11
Time lapse after trans- plantation – months (Czas, jaki upłynął od przeszczepu – miesiące)	37.4 ± 25	28.1 ± 21	40.1 ± 20.9	35.7 ± 26.3	26 ± 36.8
Oral hygiene index PI + CI (Wskaźnik higieny jamy ustnej)	2.28 ± 1.02	1.83 ± 0.58	1.52 ± 0.80**	1.49 ± 0.78***	0.83 ± 0.36

* p < 0.04 group 1 and 2 vs. group 3.

** p < 0.02 group 1 vs. group 3.

*** p < 0.002 group 1 vs. group 4.

* p < 0,04 grupa 1 i 2 względem grupy 3.

** p < 0,02 grupa 1 względem grupy 3.

*** p < 0,002 grupa 1 względem grupy 4.

transplantation in groups of patients with and without GH was similar. On the other hand, total yearly dosage of CsA in patients from group with GH as compared to group without GH was significantly higher. In a group of 80 patients treated with verapamil, GH was found in 28 patients (35%). Out of 17 patients treated with amlodipine 8 patients (47%) suffered from GH.

The index of oral hygiene was significantly higher in patients with GH than in patients without GH. The lowest index was found in patients treated with tacrolimus; PI + CI – 0.83 ± 0.36. In the group treated with tacrolimus combined with MMF and P, where patients at the same time received amlodipine GH was not found. The most common antigens HLA antigens class II in the

Table 2. Clinical data of patients with different degree gingival hyperplasia**Tabela 2.** Dane kliniczne pacjentów z przerostem dziąseł różnego stopnia

	Group 1 (Grupa 1)	Group 2 (Grupa 2)	Group 3 (Grupa 3)	Group 4 (Grupa 4)
CsA trough level within 12 months post transplant (Stężenie CsA w ciągu pierwszych 12 miesięcy po przeszczepie) ng/ml	231 ± 42	231 ± 39	236 ± 41	238 ± 40
Total CsA dosage in the first year post transplant (Całkowita dawka CsA w pierwszym roku po przeszczepie) g	90 ± 34	90 ± 23	75 ± 19	81 ± 26
Total CsA dosage (Całkowita dawka CsA) g	234 ± 162	182 ± 114	186 ± 70	183 ± 121

studied population were HLA-DR5, -DR1, -DR2 and -DR3; -DR8 being the least common. Allele HLA-DR2 was present in almost half of the patients (48.6%) suffering from GH. Allele HLA-DR2 was seen in 60% of patients with severe GH. HLA-DR1 was considerably less common in patients with GH than in patients without GH. Creatinine levels in particular groups of patients did not differ and were 1.2–2.1 mg/dl. No correlation was seen between kidney function and GH.

All patients, with second and third degree of GH who were converted to tacrolimus therapy, exhibited a slow decrease in gingival thickness. The strongest decrease in gingival thickness occurred between 3–4 months after switching to tacrolimus. After one-year tacrolimus treatment full regression of GH was found.

Discussion

Gingival hyperplasia was observed in 46% of patients after kidney transplantations treated with CsA while no patients treated with tacrolimus exhibited GH. According to research presented by other authors the frequency of GH in patients treated with CsA was assessed at 30–50% [8]. The correlation between CsA trough level and GH in the first year after transplantation was not found. Certainly, there were some differences in the free medicine level. Free medicine concentration determines both immunosuppressive and toxic effect of CsA. Significant correlation was found between CsA dosage in the first year after transplantation and GH. The studies on the subject which have been published so far do not include any assessment of cumulated CsA dosage impact upon GH; the results of correlation between CsA level in blood and GH being controversial. CsA concentration and its metabolites examined in gingival pocket liquid did not correlate with GH; however the scope of this study needs to be extended.

Thomas et al. [9], in recently published study comprising 236 patients, showed significant correlation between CsA concentration in blood 6 and 12 months after kidney transplantation and GH. Higher frequency and severity of GH in patients after heart transplantation where larger dosage of CsA was applied than in case of kidney transplantation also seemed to confirm CsA dosage affect [10].

Twice as frequent occurrence of GH in men than in women may indicate a reaction of CsA with sex hormones and gingivae connective tissue components. Thomason et al. found increased sensitivity to GH among younger men [11]. The authors also draw one's attention to higher fre-

quency of GH in children and adolescents as compared to adults.

Calcium channel blockers are an important group of drugs widely used in CsA nephrotoxicity prevention as well as in hypertension treatment. In this group of drugs nifedipine is responsible for GH in 15–85% of patients [3]. High frequency of GH affecting 90–100% of gingival units was found in patients treated with amlodipine (50%). Amlodipine accumulates in gingival pocket liquid stimulating local periodontal pathology. Indeed higher concentration of these medicines is seen in places of inflammation, which induces local GH [12]. Gingival overgrowth was seen in 35% of patients treated with verapamil and CsA. This is not much different from the data quoted in other studies for patients treated only with CsA. Therefore, it appears that verapamil has no additional influence upon GH. Cebeci et al. [13] carried out comparative research of CsA influence used as the only medicine and CsA plus verapamil combination influence. They have found GH in 28.9% of patients treated only with CsA and 34% of patients treated with CsA combined with verapamil.

While searching for factors responsible for GH induced by drugs, attention was paid to HLA phenotype [2]. It has been suggested that the major histocompatibility complex genes may change inflammatory response in gingivae tissue as well as medicines metabolism. High frequency of HLA-DR2 and significantly less common occurrence of HLA-A3 and HLA-DR1 alleles was found. Similarly, research of HLA-DR alleles distribution made in authors' centre proved high frequency of DR2 antigen occurrence in patients with GH. DR2 antigen was found in almost half of the patients with GH and in 27% of patients without GH. It is suggested that HLA-DR2 should be a risk factor of GH. Patients with this allele suffered from GH twice as often as patients with HLA-DR1. GH distribution was high among patients with DR7 antigen.

Transforming growth factor β 1 (TGF- β 1) may be one of the factors responsible for pathogenesis of GH. The study of TGF- β 1 showed intensive expression of the growth factor at the tips of dermal papillae of the overgrown gingivae. Fibroblasts coming from overgrown gingivae were more sensitive to TGF- β 1 and they were also responsible for increased protein synthesis of extracellular matrix (ECM) [14]. ECM proteins accumulation is the basis for GH stimulated by CsA. TGF- β 1 is not the only factor responsible for GH induced by CsA. Recent studies showed increased expression of other cytokines such as PDGF (platelet-derived growth factor) and IL-6.

The patients treated with tacrolimus, did not suffer from GH despite the fact that half of the patients received amlodipine which intensifies GH, and prevalence of HLA-DR2 antigen was similar as in group of patients treated with CsA. Differences in effect of the two inhibitors of calcineurine is that tacrolimus can selectively block receptors function

for TGF- β 1. This study demonstrated that switching therapy from CsA to tacrolimus reverses CsA-induced GH. The association between GH and CsA as well as regression of hyperplasia after switching CsA therapy to tacrolimus found in this study is an indication to convert CsA to tacrolimus in patients with initial GH.

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