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Clinical Status of Marginal Gingiva in Renal Transplant Recipients Treated with Calcineurine Inhibitors and Calcium Channel Blockers

Stan kliniczny dziąseł u pacjentów po przeszczepieniu nerki
leczonych inhibitorami kalcyneuryny
i lekami blokującymi kanał wapniowy

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Abstract

Background. Renal transplantation is a method of treating chronic renal failure. Gingival overgrowth is a common side effect of immunosuppressive treatment with cyclosporine A. Concomitant use of calcium channel blockers also causes gingival overgrowth or intensifies it. Tacrolimus is a new inhibitor of calcineurine used as an alternative to cyclosporine A.

Objectives. Periodontal status: oral hygiene, gingivitis degree as well as extent and level of gingival overgrowth were evaluated.

Material and Methods. In the study, 124 renal transplant recipients were treated with cyclosporine A and 38 with tacrolimus. At the same time, patients were given calcium channel blockers. Impact of age, sex, calcineurine inhibitors dosage, sort of calcium channel blocker used as well as duration of gingival overgrowth treatment were studied.

Results. Gingival overgrowth of different degree was present in 58 renal transplant recipients (46.7%) treated with CsA and in none of the patients treated with tacrolimus. Hygiene and inflammation indices were significantly higher in the group of patients with gingival overgrowth as compared to the group without gingival overgrowth treated with CsA. In the group of patients treated with tacrolimus, these indices were the lowest, and the gingivae were sort of shrunk and pale.

Conclusions. Patients with risk factors in gingival overgrowth and patients with severe overgrowth should be converted to tacrolimus treatment (**Dent. Med. Probl. 2005, 42, 2, 233–239**).

Key words: renal transplantation, cyclosporine A, tacrolimus, gingival overgrowth.

Streszczenie

Wprowadzenie. Przeszczepienie nerek jest metodą leczenia przewlekłej niewydolności tego narządu. Przerost dziąseł występuje jako działanie uboczne immunosupresyjnego leczenia cyklosporyną A. Równolegle stosowane leki blokujące kanał wapniowy również powodują powstawanie przerostu dziąseł lub zwiększają jego intensywność. Takrolimus jest nowym inhibitorem kalcyneuryny stosowanym alternatywnie do cyklosporyny A.

Cel pracy. Ocena stanu przyzębia brzeżnego, higieny jamy ustnej, stopnia zapalenia dziąseł, rozległości i stopnia przerostu dziąseł u pacjentów po przeszczepieniu nerki.

Materiał i metody. W przeprowadzonych badaniach 124 pacjentów po przeszczepie nerki było leczonych cyklosporyną A, a 38 takrolimusem. Chorzy równolegle otrzymywali leki blokujące kanał wapniowy. Zbadano wpływ wieku, płci, dawki inhibitorów kalcyneuryny, rodzaju stosowanego leku blokującego kanał wapniowy oraz czasu leczenia na przerost dziąseł.

Wyniki. Przerost dziąseł różnego stopnia wystąpił u 58 pacjentów po przeszczepieniu nerki (46,7%) leczonych CsA i u żadnego z leczonych takrolimusem. Wskaźniki higieny i zapalenia były znacząco wyższe w grupie pacjentów leczonych CsA z przerostem dziąseł w porównaniu do grupy bez przerostu. W grupie lezonej takrolimusem wskaźniki te były najniższe, a dziąsła obkurczone i blade.

Wnioski. Pacjenci ze stwierdzanymi czynnikami ryzyka przerostu dziąseł oraz ze stwierdzanym znacznym przerostem dziąseł powinni być leczeni takrolimusem (**Dent. Med. Probl. 2005, 42, 2, 233–239**).

Słowa kluczowe: przeszczep nerki, cyklosporyna A, takrolimus, przerost dziąseł.

Renal transplantation is a method of treating chronic renal failure. Thanks to new immunosuppressive drugs, which inhibit immunological response, the function of the transplanted organ, one year after the surgery, is in many medical centres restored to over 90% [1]. The problem one is confronted with now is the long-term immunosuppressive treatment.

Cyclosporine A (CsA) was first used to prevent allograft rejection following renal transplantation in 1978. Its side-effects have been carefully described and documented: hypertension, nephrotoxicity, hyperlipidemia, hirsutism, neurotoxicity and gingival hyperplasia [2]. Gingival overgrowth is the common side effect of immunosuppressive treatment with cyclosporine A. The pathological changes in kidney transplant recipients were first observed by Starzl in 1980. First cases of gingival hyperplasia associated with cyclosporine A treatment were described in dental magazines in 1983 [3]. Clinically found gingival overgrowth is present with different intensity in 8 to 85% of patients; teeth always being present, toothless process excluded [4, 5]. CsA is used as oil solution called Sandimmun and as microemulsion formation labelled Neoral. Neoral has better bioaccessibility and smaller pharmacokinetic variability hence better effectiveness than Sandimmun. This is why Neoral is used by most transplantation centres [6].

In late 90's, a new calcineurine inhibitor was introduced, namely tacrolimus (FK-506) [7]. Tacrolimus is a macrolid immunosuppressive drug used as an alternative to cyclosporine A. Despite differences in chemical structure, working mechanism, clinical effectiveness and side-effects of both drugs are similar. Tacrolimus more often causes diabetes mellitus, neurological side-effects such as tremor or headache, and gastrointestinal complaints such as diarrhoea or cramping. Unlike CsA it causes hair loss leading to alopecia, and it does not have any impact upon gingival overgrowth [8].

For over 20 years, research has been carried out on gingival overgrowth risk factors as a side-effect of immunosuppressive treatment with cyclosporine A. However, the definite cause of this pathology has not been found yet. Attention has been paid to local risk factors of gingival overgrowth, namely dental plaque presence, gingivitis, unfavourable anatomical conditions or pretransplant hyperplasia, to the connection of oral cavity hygiene and gingivitis degree with the extension and degree of gingival overgrowth [4, 9] (Fig. 1).

Not always has positive correlation between these factors and gingival overgrowth been found. Nevertheless, gingival inflammation and plaque

were strongly associated with gingival overgrowth [3, 9, 10] (Fig. 2). In the research conducted by Pilatti and Sampaio [11], statistically significant, smaller gingival overgrowth was found in rats, in the group with CsA-induced gingival overgrowth with local application of chlorhexidine.

Relationship between gingival overgrowth and age, sex, cyclosporine A dosage, treatment duration and medicine level in blood have been studied [12–14].

Attention has also been paid to pharmacokinetic properties of applied medicines seen as risk factors in gingival overgrowth [15, 16]. No correlation between gingival overgrowth and the examined pharmacokinetic CsA parameters has been found. The connection between gingival overgrowth and CsA dosage, its concentration and treatment duration is still unclear. Research results conducted for many years vary considerably. The connection between CsA dosage and gingival overgrowth is also confirmed by the frequency of gingival overgrowth in the first year after transplantation, when CsA level is higher than later on. On the other hand, it may also suggest hypersensitivity to CsA that occurs in the first months of treatment.

Dihydropyridines (calcium channel blocking agents) are an important group of drugs commonly used in CsA nephrotoxicity prevention and in hypertension treatment, 60% to 80% of patients after kidney transplant suffer from. The drugs initiate and/or intensify gingival overgrowth [15, 17]. Permeation of nifedipin and amlodipin into the gingival crevicular fluid (GCF) has also been found [4].

Verapamil suppresses cellular immunity and it exerts synergistic with CsA immunosuppressive effect on the proliferation of T lymphocyte and by changing CsA metabolism, it increases CsA level in blood.

In further research, gingival crevicular fluid (GCF) contents has been assessed in patients with gingival overgrowth treated with CsA. It has been found that CsA therapy does not directly increase IL-1 β and IL-6 cytokines levels in GCF. It has been put forward that changing levels of these interleukins can have an impact on gingival overgrowth, this also being linked to the inflammation [18]. Buduneli et al. found significantly elevated level of the plasminogen activator (PA) in GCF obtained from sites with severe gingival overgrowth [19].

Gingival overgrowth induced by medicines is present only in a group of patients, who seem to be prone to this disorder. Attention is also paid to genetic conditioning of the overgrowth. Distribution of HLA antigen class I and II in patients

treated with CsA and/or calcium channel blockers. It has been suggested that HLA-DR1 has a protective influence upon the overgrowth whereas HLA-DR2 increases the overgrowth risk [20]. Also donor-host mismatching may contribute to this pathology.

The latest research carried out on a group of 146 patients after kidney transplant treated with CsA combined with calcium channel blockers has shown the impact of TGF- β_1 gene polymorphism on gingival overgrowth. This polymorphism represents independent genetic determination of gingival overgrowth [21]. Moreover, increased production of TGF- β_1 is associated with this polymorphism.

TGF- β_1 is a multifunctional inflammation mediator capable of controlling proliferation, that is growing and differentiation of cells. What is more, it activates the gene of expression for the synthesis of extracellular matrix ingredients containing collagen proteins [22]. Quantitative and qualitative differences of TGF- β_1 isoform and the expression of its receptors in overgrown gingivae fibroblasts have been found. This may be linked to gingival overgrowth pathogenesis. CsA stimulates T lymphocytes and endothelium cells to free TGF- β_1 . According to the researchers, it affects both CsA effectiveness and its toxicity. Research by Buduneli et al. [23] on TGF- β_1 level gingival fluid confirms the theory that CsA causes increased synthesis of TGF- β_1 in gingival fluid. However, Buduneli also puts forward that this is not the only factor responsible for gingival overgrowth present in patients suffering from gingival overgrowth treated with CsA. Ultrastructural studies revealed an increased production of amorphous ground substance by fibroblasts, but the exact mechanism is still unknown. On the other hand, it appears that tacrolimus does not influence TGF- β_1 production [24].

The aim of the study was clinical evaluation of marginal periodontium condition in renal transplant recipients treated with cyclosporine A or tacrolimus and concomitantly with calcium channel blockers.

Material and Methods

Research conducted in the years 1994–2002 involved patients from the Department of Nephrology and Transplantation in Wrocław Medical University. These patients had kidneys transplanted from cadaver donor between 1985 and 2002. In treatment of 124 patients, cyclosporine A combined with azathioprine (Aza) was used or else mycophenolate mofetil (MMF) combined with corticosteroids (P). Dosage and trough levels of CsA

depended upon the time lapse after transplantation. During the induction, patients received 8 to 12 mg/kg CsA and in the maintenance treatment 1.8 to 4 mg/kg CsA. In the treatment, the next 38 patients were given tacrolimus, CellCept and corticosteroids. At the same time patients were given calcium channel blockers.

Degree of gingival overgrowth was assessed on a four-degree scale: 0 – no overgrowth; 1 – faint interdental papilla overgrowth; 2 – marginal gingivae and interdental papilla overgrowth reaching 1/3 of the teeth crowning; 3 – marginal gingivae and interdental papilla overgrowth reaching above half of the teeth crowning.

Also, the extensiveness of the overgrowth and the number of the gingival units affected were evaluated and expressed in percentages. The patients were divided into four groups, depending upon overgrowth prevalence: group I – 3rd, 2nd and 1st degree of overgrowth affecting 100–51% of gingival units; group II – 3rd, 2nd and 1st degree of overgrowth affecting 50 and less than % of gingival units; group III – patients with zero or marginal 1st degree of overgrowth affecting single (up to 5) gingival units; group IV – tacrolimus treated patients.

CsA concentration in whole blood was tested by means of RIA method with the use of monoclonal antibodies; TDX method has been used since 1993, also with the use of monoclonal antibodies. In the examined groups, average concentration of CsA/tacrolimus and total average CsA/tacrolimus dosage in the first year after transplantation was assessed.

Also, the influence of calcium channel blockers (nifedipin, nitrendipin, verapamil and amlodipin), which patients received combined with CsA or tacrolimus upon gingival overgrowth was analysed. Age and sex of patients were evaluated. Oral cavity hygiene level was assessed with the use of Löe and Silness Plaque Index (PI) and inflammation with the use of Sulcus Bleeding Index (SBI) by Mühleman and Son. Clinical data of the patients are presented in Table 1.

Statistical Analysis

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

Results

Gingival overgrowth of different degree was present in 58 patients (46.7%) treated with CsA.

Table 1. Clinical data of investigated groups**Tabela 1.** Dane kliniczne badanych grup

	Group I (Grupa I)	Group II (Grupa II)	Group III (Grupa III)	Group IV (Grupa IV)
Number of patients (Liczba pacjentów)	36	22	66	38
Sex (Płeć)	5F/31M	10F/12M	29F/37M	16F/22M
Age – years (Wiek – lata)	40.5 ± 10.3	40.1 ± 11	41 ± 12.9	38.2 ± 11.3
Time lapse after transplantation – months (Czas, jaki upłynął od przeszczepu – miesiące)	33 ± 23.4	40.1 ± 20.9	35.7 ± 26.3	21 ± 9.3
CsA/tacrolimus trough level within first year after transplantation (Poziom CsA/takrolimusu w pierwszym roku po przeszczepie) ng/ml	231 ± 39	236 ± 41	238 ± 40	10.2 ± 1.8
Total average CsA/Tacrolimus dosage in first year after transplantation (Całkowita średnia dawka CsA/takrolimusu w pierwszym roku po przeszczepie) g	89 ± 28*	75 ± 19	81 ± 26	2.6 ± 1.33
PI index (Wskaźnik PI)	2.0 ± 0.8	1.52 ± 0.8**	1.49 ± 0.78***	0.83 ± 0.36
SBI index (Wskaźnik SBI)	0.85 ± 0.74*	0.40 ± 0.42	0.20 ± 0.36	0.1 ± 0.07

* $p < 0.04$ group I vs. group II, ** $p < 0.02$ group I vs. group II, *** $p < 0.002$ group I vs. group III.

• $p < 0.002$ group I vs. group II, $p < 0.0001$ group I vs. group III, $p < 0.04$ group II vs. group III.

* $p < 0,04$ grupa I vs. grupa II, ** $p < 0,02$ grupa I vs. grupa II, *** $p < 0,002$ grupa I vs. grupa III.

• $p < 0,002$ grupa I vs. grupa II, $p < 0,0001$ grupa I vs. grupa III, $p < 0,04$ grupa II vs. grupa III.

Large overgrowth of 2nd and 3rd degree comprising from 51 to 100% of gingival units was found in 36 patients (29%). Average CsA level in whole blood in the first year after transplantation and total yearly dosage of CsA in groups of patients with and without gingival overgrowth was similar. Gingival overgrowth occurred more often in patients who received CsA combined with nifedipin. Out of 22 patients treated with nifedipin, 19 (86%) suffered from gingival overgrowth. In a group of 80 patients treated with verapamil, gingival overgrowth was found in 28 patients (35%). Out of 17 patients treated with amlodipin, 8 patients (47%) suffered from gingival overgrowth. The group of patients treated with tacrolimus did not suffer from gingival overgrowth despite the fact that the 23 (60%) patients received calcium channel blockers: 6 – verapamil, 8 – nitrendipine and 9 amlodipine – overgrowth increasing factors. No connection was seen between age of patients and gingival overgrowth. The overgrowth was three times more frequent in men. Hygiene index was significantly higher in the groups of patients with gingival overgrowth as compared to the group without gingival overgrowth treated with CsA. The bleeding index

value SBI decreased along with the diminishing of gingival overgrowth, and it was also statistically higher in group I in comparison with groups II and III. In the group of patients treated with tacrolimus hygiene and inflammation indices were the lowest. The marginal parodontium was clinically healthy whereas the gingivae were sort of shrunk and pale.

Discussion

Gingival overgrowth is a serious problem in patients after transplantation who received maintenance CsA treatment. It usually begins at the interdental papilla, and then, in later stages it affects the entire gingivae and extends coronally. It occurs by all tooth surfaces, more often from the side of oral vestibule than oral cavity. No differences in intensity and extensiveness of the overgrowth were found in the upper and lower jaw [4]. It causes unsightly appearance, feeling of pain and discomfort; it hinders chewing of food, restrains patients from keeping their oral cavities clean so it supports inflammation of various intensity. All of this results in a greater risk of infection and a higher



Fig. 1. Third degree of gingival overgrowth without inflammation

Ryc. 1. Przerost dziąseł trzeciego stopnia bez stanu zapalnego



Fig. 2. Third degree of gingival overgrowth with inflammation

Ryc. 2. Przerost dziąseł trzeciego stopnia z obecnością stanu zapalnego

incidence of caries and periodontitis and also results in severe reduction of life quality [14, 25].

In the conducted research, gingival overgrowth was found in 46.7% of patients treated with CsA. In 23 patients, it was located in the front teeth section; in 5 patients it was located in the side-teeth section; in other patients, it was generalized. In an anamnesis, 4 patients claimed they had large generalized overgrowth at the beginning of

the treatment (4 to 5 months after transplantation). In two of them, the overgrowth regressed completely and in two others it decreased and affected only front teeth section. One patient had to undergo gingivectomy in places of largest hypertrophy in side-teeth section. After three months gingival overgrowth was seen again, and the patient's hygiene was proper.

In patients from group I and II, basic peri-



Fig. 3 and 4. CsA-induced gingival overgrowth

Ryc. 3 i 4. Przerost dziąseł związany z leczeniem CsA



Fig. 5 and 6. Regression of gingival overgrowth after conversion to tacrolimus, after 2 years (the same patient)

Ryc. 5 i 6. Regresja przerostu dziąseł po zmianie CsA na takrolimus po 2 latach (ten sam pacjent)

odontal therapy (scaling, deep scaling, hygiene teaching, topically applied antiseptics) was performed, which improved the clinical condition of the overgrown gums. Swelling, bleeding and degree of inflammation decreased. Prevalence and the level of overgrowth did not decrease, however it was hard and fibrous. The patients felt more comfortable. Also, earlier studies by different authors draw our attention to the connection between oral cavity hygiene, degree of gingivitis and the extent and severity of gingival overgrowth [3, 4, 11]. Furthermore, good effects of early periodontal therapy are discussed [25]. But optimal oral hygiene alone is not sufficient to reduce hyperplasia.

In our research, significant correlation of average SBI index value in group with gingival overgrowth and group without gingival overgrowth was seen. SBI decreased along with the diminishing of gingival overgrowth, and it was also statistically higher in group I in comparison with groups II and III. Lately, it was concluded that CsA-induced gingival overgrowth may be connected with individual sensitivity of each patient and it does not have to be always correlated with periodontal status [26].

During a one-year observation of six patients with extensive gingival overgrowth associated with earlier use of CsA, it was found out that the overgrowth was gradually decreasing after conversion to tacrolimus. The most conspicuous reduction of the overgrowth was observed three or four months after the change of the medicine (Fig. 3–6). Similar observations were described by Thorp et al. [8] and Hernandez et al. [27]. Also interruption of CsA therapy leads to partial or almost complete regression of gingival overgrowth in a few months [28].

It has been found that gingival overgrowth is more frequent in men than in women, which can indicate the interaction of CsA and sex hormones. Similar findings were described by Spratt and co-workers [5]. Also, Thomason et al. [4] have seen increased sensitivity to gingival overgrowth, especially among young males.

Thomson and co-workers have found that nifedipin combined with CsA caused significantly higher gingival overgrowth than only CsA in patients after heart transplantation. In our centre, since mid 90s instead of nifedipin other calcium channel blockers have been used such as amlodipin, verapamil and nitrendipin. High frequency of gingival overgrowth affecting 90–100% of dental units was found in patients treated with amlodipin (50%). The number of patients treated with amlodipin combined with CsA was small and this is why further research is necessary to confirm this conclusion. Both nifedipin and amlodipin accumulate in gingival pocket liquid stimulating local periodontal pathology. Indeed higher concentration of these medicines is seen in places of inflammation, which induces local gingival overgrowth [12].

To sum up, we must say that the results of the study show high frequency of gingival overgrowth in kidney transplant recipients treated with CsA. The frequency increases even more in patients treated with nifedipin and amlodipin at the same time. Also, the level of inflammation is associated with gingival overgrowth severity. None of the patients treated with tacrolimus, even combined with amlodipin, suffered from gingival overgrowth. Patients with risk factors of gingival overgrowth and patients with severe overgrowth should be converted to tacrolimus treatment.

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