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Conversion from Cyclosporine/Azathioprine to Tacrolimus/Mycophenolate Mofetil in Patients with Allograft Dysfunction and Cyclosporine-induced Side Effects

Konwersja cyklosporyny/azatiopryny do takrolimusu/mykofenolanu mofetilu u pacjentów z dysfunkcją alloprzeszczepu i objawami ubocznymi cyklosporyny

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Abstract

Background. Conversion from cyclosporine (CsA) to tacrolimus (Tac) can be a strategy in kidney transplant patients with acute rejection and deterioration of renal function. Cyclosporine-induced side effects can also suggest such a procedure.
Objectives. To examine the influence of conversion from CsA/azathioprine to Tac/mycophenolate mofetil (MMF) on renal graft function, survival, and cyclosporine-induced side effects.
Material and Methods. A total of 88 patients were converted to Tac/MMF for the following reasons: 55 patients (group I) in whom acute rejection had not resolved, 26 patients (group II) with chronic allograft dysfunction, and 7 patients (group III) with gingival hyperplasia or hyperlipidemia.
Results. In group I, acute rejection was treated with methylprednisolone and additionally with ATG in 10 patients. The conversion was performed 4.4 ± 5.2 months after transplantation. Serum creatinine dropped from 3.02 ± 1.6 mg/dl before conversion to 2.08 ± 0.8 ($p = 0.0002$) after 6 months, 2.2 ± 1.1 ($p = 0.003$) after 12 months, and 2.3 ± 1.4 ($p = 0.04$) after 24 months. The decline in renal function caused loss of graft in 5 patients 1 year after conversion (graft survival: 91%), in 7 after 2 years, and in 3 after 3 years (graft survival: 71%). Group II patients were converted 51.1 ± 39.7 months after transplantation and exhibited deterioration of renal function: creatinine level rose from 2.7 ± 0.6 mg/dl before conversion to 3.5 ± 1.3 mg/dl after one year ($p < 0.05$). Twelve patients lost their grafts one year after conversion (graft survival: 53.8%). Group III patients were converted 31.8 ± 28 months after transplantation and had a mean serum creatinine level of 1.1 ± 0.6 mg/dl, which did not change with conversion. The side effects of cyclosporine ameliorated. In all the patients the cholesterol level decreased from 6.06 ± 1.7 mM to 5.15 ± 1.2 mM ($p = 0.0007$) and triglyceride level from 2.45 ± 1.7 mM to 1.91 ± 1.0 mM ($p < 0.05$) 12 months after conversion. Significant changes in blood pressure were not observed after conversion.
Conclusions. The patients with acute rejection in whom antirejection therapy did not provide total resolution benefited from the conversion to tacrolimus/MMF. However, it failed to stop progressive chronic graft nephropathy. The conversion allowed regression of cyclosporine-induced side effects. Hyperlipidemia was also significantly ameliorated (**Adv Clin Exp Med 2007, 16, 2, 221–227**).

Key words: kidney transplant, conversion from cyclosporine to tacrolimus, chronic allograft nephropathy, acute rejection, cyclosporine side effect.

Streszczenie

Wprowadzenie. Konwersja cyklosporyny (CsA) do takrolimusu (Tac) u pacjentów po przeszczepie nerki może być postępowaniem w przypadku epizodu ostrego odrzucania i pogorszenia funkcji przeszczepu. Objawy uboczne cyklosporyny mogą również sugerować zmianę leczenia.

Cel pracy. Zbadanie wpływu konwersji CsA/azatiopryny do Tac/mykofenolanu mofetilu (MMF) na funkcję przeszczepu, przeżycie oraz efekty uboczne cyklosporyny.
Materiał i metody. Chorzy (88 osób) zostali skonwertowani do Tac/MMF z następujących powodów: grupa I (55 osób), u których ostre odrzucanie nie zostało skutecznie wyleczone, grupa II (26 osób) z przewlekłą nefropatią alloprzeszczepu i grupa III (7 osób) z przerostem dziąseł lub hiperlipidemią.
Wyniki. W grupie I, ostre odrzucanie było leczone metyloprednizolonem i dodatkowo u 10 osób ATG. Konwersja została przeprowadzona 4,4 ± 5,2 miesiąca po przeszczepie. Kreatynina w surowicy krwi spadła z 3,02 ± 1,6 mg/dl przed konwersją do 2,08 ± 0,8 (p = 0,0002) po 6 miesiącach, 2,2 ± 1,1 (p = 0,003) po 12 miesiącach i 2,3 ± 1,4 (p = 0,04) po 24 miesiącach. Roczne przeżycie przeszczepu po konwersji wynosiło 91%. W grupie II chorzy zostali skonwertowani 51,1 ± 39,7 miesięcy po przeszczepie. Obserwowano pogarszanie funkcji przeszczepu pomimo konwersji. Dwunastu chorych utraciło przeszczep w ciągu roku od zmiany leczenia. W grupie III chorzy zostali skonwertowani 31,8 ± 28 miesiąca po przeszczepie. Stężenie kreatyniny po konwersji nie zmieniło się. Obserwowano ustępowanie objawów ubocznych indukowanych cyklosporyną. U wszystkich pacjentów stężenie cholesterolu oraz trójglicerydów obniżyło się po konwersji. Nie obserwowano znaczących zmian ciśnienia tętniczego.
Wnioski. Chorzy z epizodem ostrego odrzucania, u których terapia przeciwodrzuceniowa nie przyniosła spodziewanego rezultatu odnieśli korzyść po konwersji do Tac/MMF. Konwersja nie powstrzymała postępu przewlekłej nefropatii przeszczepu. Obserwowano regresję objawów ubocznych indukowanych cyklosporyną oraz korzystny wpływ konwersji na hiperlipidemię (**Adv Clin Exp Med 2007, 16, 2, 221–227**).

Słowa kluczowe: przeszczepienie nerki, konwersja CsA do Tac, przewlekła nefropatia przeszczepu, ostre odrzucenie, objawy uboczne cyklosporyny.

Renal transplantation has become a successful method of treatment of end-stage renal disease (ESRD). Improvements in immunosuppression, appropriate procedures in reactions to acute rejection episodes, and our understanding of the immunological and non-immunological factors of chronic allograft nephropathy have resulted in better outcomes in graft survival. The introduction of the calcineurin inhibitor cyclosporine in the early 1980s changed one-year graft survival from 60% to 85%. In the 1990s, another, newer calcineurin inhibitor, tacrolimus, resulted in a decrease in the incidence of acute rejection [1]. Conversion from cyclosporine (CsA) to tacrolimus (TAC) in patients with renal-function deterioration due to acute or chronic rejection is a strategy to improve graft function. Cyclosporine-induced adverse effects (lipid disorders, gingival hyperplasia, hypertrichosis, hypertension) are also indications for conversion to TAC.

In the past few years the frequency of acute graft rejection (AGR) has decreased from 50–70% to 10–20%. This must have an influence on chronic graft failure. From another point of view, chronic allograft nephropathy is defined as progressive loss of renal function and is responsible for 27–40% of all graft failures between one and three years after allograft transplantation [2]. The purpose of this study was to report the present authors' experience with TAC as a replacement therapy after conversion from cyclosporine. This was expected to improve graft function by reducing acute-resistant rejection and chronic allograft nephropathy or to stop the progression of cyclosporine-induced side effects.

Material and Methods

The study encompassed 88 patients who received transplants between 1999 and 2005 at the Wroclaw Medical University. All patients received cadaveric organs. The initial treatment consisted of cyclosporine (Neoral), azathioprine, and corticosteroids (Encorton). The CsA dose was adjusted according to the through level, which was time dependent, and ranged from 250 to 300 ng/ml in the first three months, 200 to 250 ng/ml from the third to the twelfth month, and 100 to 150 ng/ml after the first year after transplantation. The azathioprine doses were tapered from 3 mg/kg on the first day to 1 mg/kg by the sixth week after transplantation. Corticosteroids were administered in doses gradually tapered to 10 mg per day over the first 180 days after transplantation.

The patients were converted to tacrolimus (Prograf) and mycophenolate mofetil (MMF, CellCept) for the following reasons: group I (55 patients), in whom acute rejection had not resolved, group II (26 patients), with chronic allograft dysfunction, and group III (7 patients), with gingival hyperplasia or hyperlipidemia (Table 1). The daily dose of tacrolimus was adjusted to the time-dependent through level, ranging from 15–18 ng/ml in the first month, 12–16 ng/ml from the second to third month, 8–12 ng/ml after the third month, 6–8 after the sixth, and 5–7 ng/ml after 12 months. MMF was administered at 2000 mg per day.

Acute graft rejection (AGR) episodes were diagnosed on the basis of clinical and biopsy evidence and were treated with methylprednisolone at a dose of 500 mg for three days. In case of corticoresistant AGR, antithymocyte globulin (ATG) was administered. The efficacy and safety of the

Table 1. Clinical data

Tabela 1. Dane kliniczne

	Group I (Grupa I)	Group II (Grupa II)	Group III (Grupa III)
Number of patients (Liczba pacjentów)	55	26	7
Age – years (Wiek – lata)	41 ± 12	41 ± 10	31 ± 28
Mean time between transplantation and conversion – months (Średni czas między przeszczepieniem a konwersją – miesiące)	4.4 ± 5.2	51.1 ± 39.7	31.8 ± 28
Cold ischemia time – h) (Czas zimnego niedokrwienia – godz.)	26 ± 7	25 ± 8	21 ± 5.8
Mean waiting time between first dialysis and transplantation – months (Średni czas oczekiwania po pierwszej dializie na przeszczepienie – miesiące)	29 ± 25	34 ± 31	15 ± 11
Mean number of mismatches (Średnia liczba niezgodności HLA)	3.0 ± 0.8	3.0 ± 1.0	3.5 ± 1.3
PRA over 20% (PRA ponad 20%)	11% of patients	17% of patients	0% of patients
Cyclosporine level before conversion – ng/ml (Stężenie cyklosporyny przed konwersją – ng/ml)	237 ± 70	130 ± 50	140 ± 10
Tacrolimus level 3 months after conversion – ng/ml (Stężenie takrolimusu 3 miesiące po konwersji – ng/ml)	7.9 ± 2.0	7.5 ± 3.3	7.8 ± 2.4
Tacrolimus level 12 months after conversion – ng/ml (Stężenie takrolimusu 12 miesięcy po konwersji – ng/ml)	7.8 ± 3.1	6.6 ± 1.9	7.5 ± 2.9

conversion was evaluated during the follow-up, which lasted 19.0 ± 11 months for group I, 13.9 ± 14 for group II, and 16.3 ± 9 months for group III.

Data were compared using parametric tests of significance. A p-value < 0.05 was considered statistically significant. Graft and patient survival were assessed by the Kaplan-Meier method.

Results

In group I, acute rejection was treated with methylprednisolone and additionally with ATG in 10 patients. The conversion was performed 4.4 ± 5.2 months after transplantation. Serum creatinine dropped from 3.02 ± 1.6 mg/dl before conversion to 2.2 ± 1.1 mg/dl (p = 0.003) after 12 months, and 2.3 ± 1.4 mg/dl (p = 0.04) after 24 months (Table 3). One patient died due to cardiac arrest (patient survival: 98%). The decline in renal function caused loss of graft in 5 patients one year after conversion (graft survival: 91%), in another 7 after two years, and in another 3 after three years (graft survival: 71%). The one-year graft survival was comparable to the one-year graft survival in our department in 2000–2002, which was 86–93%. The three-year graft survival in 2000–2002 was 78–86%.

In group II, the patients were converted 51.1 ± 39.7 months after transplantation and exhibited deterioration in renal function: creatinine level rose from 2.7 ± 0.6 mg/dl before conversion to 3.5 ± 1.3 mg/dl after one year (p < 0.05) (Table 2).

Table 2. Serum creatinine concentration (mg/dl)

Tabela 2. Stężenie kreatyniny w surowicy (mg/dl)

	Before conversion (Przed konwersją)	After 1 month (Po miesiącu)	After 3 months (Po 3 miesiącach)	After 6 months (Po 6 miesiącach)	After 12 months (Po 12 miesiącach)	After 18 months (Po 18 miesiącach)	After 24 months (Po 24 miesiącach)
Group I (Grupa I)	3.02 ± 1.6	2.18 ± 0.8	2.11 ± 0.9	2.08 ± 0.8	2.2 ± 1.1	2.3 ± 1.08	2.3 ± 1.4
Group II (Grupa II)	2.7 ± 0.6	2.6 ± 0.7	2.68 ± 0.7	3.0 ± 1.1	3.5 ± 1.3		

p < 0.05 for group I between creatinine levels before and after conversion.

p < 0,05 dla grupy I między stężeniami kreatyniny przed i po konwersji.

Table 3. Side effects after conversion

Tabela 3. Działania uboczne po konwersji

Side effects (Działanie uboczne)	Number of patients (Liczba pacjentów)
Diarrhea (Biegunka)	6
Diabetes mellitus (Cukrzyca)	2
Hyperglycemia (Hiperglikemia)	4
Leukopenia (Leukopenia)	20
Anemia (Anemia)	16
CMV infection (Zakażenie CMV)	8
Hair loss (Utrata włosów)	0
HSV infection (Zakażenie HSV)	4
Pneumonia (Zapalenie płuc)	2
Kaposi's sarcoma (Mięsak Kaposiego)	1

A total of 12 patients lost their grafts one year after conversion (graft survival: 53.8%).

In group III, the patients were converted 31.8 ± 28 months after transplantation and had a serum creatinine level of 1.1 ± 0.6 mg/dl, which did not change after conversion. The side effects of cyclosporine ameliorated.

In all the patients the cholesterol level decreased from 6.06 ± 1.7 mM to 5.15 ± 1.2 mM ($p = 0.0007$) and the triglyceride level from 2.45 ± 1.7 mM to 1.91 ± 1.0 mM ($p < 0.05$) 12 months after conversion (Fig. 1). The systolic blood pressure (BP) before conversion was 147 ± 26 mm Hg, after 3 months 141 ± 22 mm Hg (NS), and after 12 months 141 ± 30 mm Hg (NS). Diastolic BP was 88 ± 12, 89 ± 14, and 90 ± 10 mm Hg, respectively. The patients received 2.2 ± 1.1 hypertensive drugs before conversion, 2.5 ± 1.0 after 3 months, and 2.57 ± 1.1 after 12 months.

Side effects observed after conversion to tacrolimus are shown in Table 3.

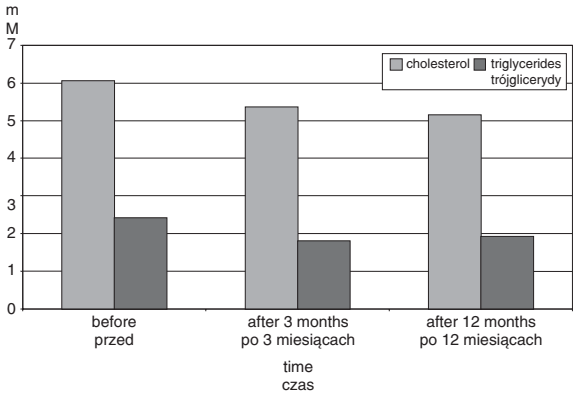

Fig. 1. Cholesterol and triglycerides after conversion

Ryc. 1. Cholesterol i trójglicerydy po konwersji

Discussion

The present authors described their experience with all patients in their department after kidney transplantation and conversion to Tac due to acute resistant rejection, chronic allograft nephropathy (CAN), or cyclosporine-induced side effects. Conversion to Tac has been shown to improve renal function in patients with resistant acute rejection, even when antilymphocyte preparations had been ineffective [3–7]. A comparison of CsA and Tac showed no difference in 5-year renal allograft survival [8], but the incidence of acute rejection was lower in patients who received Tac [9]. The experience of the present authors confirmed decreased creatininemia after conversion in a group with resistant acute rejection in whom antirejection therapy did not cause resolution. Margreiter et al. in a multicenter European study including 560 patients randomly assigned to Tac (287 patients) and CsA (273 patients) showed that biopsy-confirmed acute rejection was significantly lower in the Tac group (19.6% *vs.* 37.3%) [10]. Corticosteroid-resistant biopsy-confirmed acute rejection was reported as significantly more rare in the Tac group (27% *vs.* 57%) [10]. The rate of recurrent acute rejection was described as also significantly lower in the Tac group than in the CsA group (1.1% *vs.* 7.0%) [10]. In another prospective multicenter controlled study of patients who experienced a first episode of acute rejection while receiving a regimen based on CsA, transplant recipients were randomized to either start Tac or to continue on the CsA-based treatment. The study consisted of 61 recipients in the Tac group and 58 recipients in the CsA group. The incidence of recurrent biopsy-proven rejection was significantly lower in the Tac group (8.8%) compared with the CsA group (34.1%, $p = 0.002$) [11].

Chronic allograft nephropathy (CAN) is defined as the increasing loss of allograft function months or years after transplantation. It is not only chronic rejection, which involves immunological changes, but also non-immunological mechanisms. Immunological factors are connected with HLA matching, acute rejection (including subclinical rejection) and appropriately effective

immunosuppression. Non-immunological factors, including delayed graft function, ischemia reperfusion injury, nephrotoxicity dependent on calcineurin inhibitors, hyperlipidemia, hypertension, virus and bacterial infections, and donor brain death or donor and recipient characteristics may influence the loss of graft function. The clinical view of CAN consists of a slow decline in graft function with a decrease in GFR and increasing serum creatinine level, proteinuria, and hypertension. Biopsy is still the "gold" standard for the assessment of allograft damage. It should be considered after eliminating evident sources of dysfunction, such as CsA or Tac nephrotoxicity, dehydratation, infection, and ureteric obstruction. It is important to process the biopsy early before significant dysfunction because CAN is later less responsive to therapy. The sample should include arterioles for assessing calcineurin inhibitor-induced hyalinosis and small muscular arteries to assess immuno-mediated fibrointimal hyperplasia. Clinical information such as transplant function, donor quality, delayed graft function, acute rejection, and immunosuppression should be provided to the pathologist. In the end, collaborative clinicopathological diagnosis is needed using clinical and histological data to choose the appropriate therapy [12].

Histological changes in a biopsy show interstitial fibrosis and tubular atrophy with glomerulosclerosis along with concentric intimal thickening of arteries and arterioles [13]. Krieger et al. respectively analyzed 522 graft losses among 2140 examined transplants. Graft loss due to CAN occurred in 32% and death with functioning allograft in 34% of cases [14].

Graft function within the first year post-transplantation has been found to be an important factor in graft loss [15–19]. Hariharan et al., in a large study of 105,742 renal recipients, showed the influence of post-transplant renal function on long-term transplant survival [20]. Patients were classified according to their one-year post-transplant serum creatinine. It was shown that the one-year creatinine level is a strong predictor of transplant survival. A downward trend in graft half-life was connected with progressive increases in one-year creatinine levels. Projected median graft half-lives for cadaveric kidneys in years according to one-year post-transplant creatinine value are 14.0 years with creatinine < 1.0 mg/dl, 13.2 years with creatinine between 1.1 and 1.5 mg/dl, and 9.4 years with creatinine over 1.6 to 2.0 mg/dl.

Both calcineurin inhibitors have been observed to be associated with nephrotoxicity and contributing to late kidney dysfunction [21, 22]. However, immunosuppression with Tac resulted in significantly fewer acute rejections in comparison with CsA [21]. Even increased interstitial fibrosis has been observed in patients treated with CsA compared with Tac [23].

In the present analysis it was expected that patients with chronic allograft nephropathy may benefit by conversion from CsA to Tac. Improvement in creatininemia in patients with CAN after conversion to tacrolimus was not observed in this study. The probable reason for this lack of success was the late introduction of tacrolimus. There are other ways to prevent chronic allograft nephropathy or stop its progression, i.e. calcineurin inhibitor minimization or withdrawal connected with applying mycophenolate mofetil and calcineurin minimization or withdrawal with sirolimus or everolimus. Moreover, treatment of acute rejection and delayed graft function management as well as better control of hypertension and hyperlipidemia should be adequately managed.

Reduction of cardiovascular risk factors in patients after transplantation is important because there is a higher incidence of cardiovascular disease than in patients without a transplant. To improve long-term graft and patient survival it is important to slow the progression of atherosclerosis and try to reduce morbidity and mortality. The improvements in cholesterol and triglyceride levels were significant in the present study. Conversion to Tac has been demonstrated to improve the cardiovascular risk profile [24–26]. There are studies which indicate that Tac is associated with lower incidences of hypertension and hyperlipidemia in comparison with CsA [26–29]. In the Margreiter et al. European study mentioned above, the mean total cholesterol level in the Tac group six months after transplantation was significantly lower than in the CsA group (5.35 *vs.* 5.89) [10]. Vincenti et al., in a multicenter analysis, reported that the use of Tac instead of CsA improved the cardiovascular risk profile. The proportion of patients with hyperlipidemia (20% *vs.* 59%) was significantly lower under Tac [27]. Hohage et al. presented outcomes in patients converted from CsA to Tac because of recurrent graft rejections. Cholesterol levels decreased significantly after conversion, from 258 to 225 mg/dl [28].

Hypertension in thought to be another risk factor for cardiovascular problems in patients after transplantation. In a multicenter analysis the proportion of patients with hypertension being treated with CsA was significantly higher compared with patients on Tac (91% *vs.* 81%) [26]. Conversion from CsA to Tac in a study of 127 patients resulted in a reduction in systolic and diastolic blood pressure, leading to a reduction in the Framingham risk score from 5.7 to 4.8 ($p < 0.05$) [29].

Significant changes in systolic and diastolic blood pressure and the number of hypertensive drugs were not observed in the present analysis after the conversion to tacrolimus.

The symptoms of patients who received tacrolimus because of cyclosporine-induced side effects such as gingival hyperplasia and hypertrichosis were improved in all cases in the present analysis. The cause of gingival hyperplasia after CsA therapy has not been found. Switching to cyclosporine may be a method of the treatment [30, 31].

The authors conclude that patients with acute rejection in whom antirejection therapy did not provide total resolution benefit from the conversion to tacrolimus and MMF. However, conversion too late may fail to stop progressive chronic graft nephropathy. The conversion allows cyclosporine-induced side effects to regress. Hyperlipidemia significantly ameliorates after conversion.

References

[1] Meier-Kriesche HU, Schold JD, Srinivas TR et al.: Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. Am J Transplant 2004, 4, 378.

[2] Cecka JM: The UNOS Scientific Renal Transplant Registry. In: Clinical transplants. Eds.: Cecka JM, Terasaki PI: 2000. Los Angeles, UCLA Immunogenetics Center 2001, p 1.

[3] Jordan ML, Shapiro R, Vivas CA et al.: FK506 „rescue" for resistant rejection of renal allografts under primary cyclosporine immunosuppression. Transplantation 1994, 57, 860.

[4] Kliem V, Radermacher J, Hiss M et al.: Conversion to tacrolimus for acute corticosteroid- and antibody-resistant rejection following kidney transplantation. Transplant Proc 1999, 31, 37.

[5] Blume C, Hollenbeck M, Ivens et al.: Conversion from cyclosporine to tacrolimus prevents transplant function loss due to acute steroid-resistant or chronic rejection in renal allograft recipients. Transplant Proc. 2001, 33, 3161.

[6] Yamani MH, Starling RC, Pelegrin D et al.: Efficacy of tacrolimus in patients with steroid-resistant cardiac allograft cellular rejection. J Heart Lung Transplant 2000, 19, 337.

[7] Morrissey PE, Gohh R, Shaffer D et al.: Correlation of clinical outcomes after tacrolimus conversion for resistant kidney rejection or cyclosporine toxicity with pathologic staging by the Banff criteria. Transplantation 1997, 27, 845.

[8] Kaplan B, Schold JD, Meier-Kirsche HU: Long-term graft survival with neural and tacrolimus: a paired kidney analysis. J Am Soc Nephrol 2003, 14, 2980.

[9] Pirsh JD, Miller J, Deierhoi MH et al.: A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. FK506 Kidney Transplant Study Group. Transplantation 1997, 63, 977.

[10] Margreiter R: European Tacrolimus vs. Ciclosporin Microemulsion Renal Transplantation Study Group. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomized multicenter study. Lancet 2002, 359, 741.

[11] Dudley CR: European tacrolimus Renal Rejection Study Group: Conversion at first rejection: a prospective trial comparing cyclosporine microemulsion with tacrolimus in renal transplant recipients. Transplant Proc. 2001, 33, 1034.

[12] Nankivell BJ, Chapman JR: Chronic Allograft Nephropathy: Current Concepts and Future Directions, Transplantation 2006, 81, 643.

[13] Racusen LC, Solez K, Colvin RB et al.: The Banff 97 working classification of renal allograft pathology. Kidney Int 1999, 55, 713.

[14] Krieger N, Becker B, Heisey D et al.: Chronic allograft nephropathy uniformly affects Recipients of cadaveric, nonidentical living-related, and living-unrelated grafts. Transplantation 200, 75, 1677.

[15] Cecka JM: The UNOS Scientific Renal Transplant Registry. In: Clinical transplants Cecka. Eds.: JM, Terasaki PI 1998. Los Angeles, UCLA Tissue Typing Laboratory, 1–16.

[16] Nicol D, MacDonald AS, Belitsky P: Early prediction of renal allograft loss beyond one year. Transplant Int 1993, 6, 153.

[17] Giral M, Taddei C, Nguyen JM et al.: Single center analysis of 468 first cadaveric kidney allograft with uniform ATG-CsA sequential therapy. In Clinical Transplants 1996. Eds.: MJ Cecka, Terasaki PI, Los Angeles, UCLA Tissue Typing Laboratory, 257–264.

[18] Humar A, Kerr S, Gillingham KJ, Matas AJ: Features of acute rejection that increase risk for chronic rejection. Transplantation 1999, 68, 1200.

[19] Ishikawa A, Flechner SM, Goldfarb DA et al.: Significance of serum creatinine pattern and area under the creatinine versus time curve during the first acute renal transplant rejection. Transplant Proc 2000, 32, 781–783.

[20] Hariharan S., McBride MA, Cerikh WD et al.: Post-transplant renal function in the first year predicts long-term kidney transplant survival Kidney Int 2002, 62, 311.

[21] Pascual M, Swinford RD, Ingelfinger JR et al.: Chronic rejection and chronic cyclosporin toxicity in renal allografts. Immunol Today 1998, 19, 514.

[22] Halloran PF: Call for revolution: a new approach to describing allograft deterioration. Am J Transplant 2002, 2, 195.

[23] Murphy GJ, Waller JR, Sandford RS et al.: Randomized clinical trial of the effect of microemulsion cyclosporin and tacrolimus on renal allograft fibrosis. Br J Surg 2003, 90, 680.
[24] McCune TR, Thacker LR II, Peters TG et al.: Effects of tacrolimus on hyperlipidemia after successful renal transplantation: a Southeastern Organ Procurement Foundation multicenter clinical study. Transplantation 1998, 65, 87.
[25] Artz MA, Boots JM, Ligtenberg G et al.: Conversion from cyclosporine to tacrolimus improves quality-of-life indices, renal graft function and cardiovascular risk profile. Am J Transplant 2004, 4, 937.
[26] Baid-Agrawal S, Delmonico FL, Tolkoff-Rubin NE et al.: Cardiovascular risk profile after conversion from cyclosporine A to tacrolimus in stable renal transplant recipients. Transplantation 2004, 77, 1199.
[27] Vincenti F, Jensik SC, Filo RS et al.: A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: evidence for improved allograft survival at five years. Transplantation 2002, 73, 775.
[28] Hohage H, Welling U, Heck M et al.: Conversion from cyclosporine to tacrolimus after renal transplantation improves cardiovascular risk factors. Int Immunopharmacol 2005, 5, 117.
[29] Artz MA, Boots JM, Ligtenberg G et al.: Conversion from cyclosporine to tacrolimus improves quality-of-life indices, renal graft function and cardiovascular risk profile. Am J Transplant 2004, 4 (6), 937–945.
[30] Radwan-Oczko M, Boratynska M, Banasik M et al.: Regression of Cyclosporine A-Induced Gingival Hyperplasia Following Switch to Tacrolimus in Renal Transplant Recipients. Adv Clin Exp Med 2005, 14, 69.
[31] Kohnle M, Lutkes P, Witzke O et al.: Conversion to Tacrolimus in Cyclosporine A treated patients with gum hyperplasia. Transplant Proc 1998, 30**,** 2122.

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