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Clinical impact of non-compliance after renal transplantation

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Introduction. Non-compliance with immunosuppressants in renal transplant recipients is an important factor affecting graft survival. In the present study, we examined the prevalence of non-compliance, risk factors, as well as the long-term impact of non-compliance on the graft survival after renal transplantation (RT).

Materials and Methods. Non-compliance with medication and follow-up care was retrospectively evaluated in 197 renal transplant recipients (mean age 48.4 ± 14.6 years, 40.6% female, and 86.8% primary graft) with at least 36 months follow-up period. The diagnosis of non-compliance was based on patient self-admission to having discontinued the immunosuppressive drugs as the cause of graft dysfunction (self-report by questionnaires). Long-term graft and patient outcomes in compliant and non-compliant patients were acute rejection (AR) rate and chronic allograft dysfunction (CAD), graft and patient one and three year survival.

Results. The prevalence of non-compliance was 8.1%. Noncompliant patients had more AR episodes (50% vs 24.9%, $p = 0.03$) and CAD (43.8% vs 21%, $p = 0.04$). Risk of all cause graft failure in non-compliant group was higher, OR 4.99 (95% CI 1.55–16.08; $p = 0.006$) compared with compliant group. Graft survival at one and three years was 78.5% and 66.3%, respectively, for compliant patients, while in non-compliant patients 68.8% and 43.7% (Log Rank 7.37; $p < 0.006$). The risk factors associated with non-compliance were younger age ($p = 0.016$) and immunosuppressive regimen with the highest number of pills ($p = 0.029$).

Conclusions. Patients' compliance with medication and follow-up care after renal transplantation shows long-term clinical benefits. It is of utmost importance to develop intervention strategies to enhance compliance in this population.

Key words: renal transplantation, compliance, graft and patient outcomes

INTRODUCTION

Non-compliance toward diet, medications, regular physician visits and different recommendations is a real and common problem in medicine. Very often patients' ignorance of the immunosuppressive regimen as well as non-compliant behaviour may result in graft loss after renal transplantation (RT).

The non-compliance syndrome in transplantation can be defined as a covert non-adherence to prescribed medication used for the prophylaxis of allograft rejection and threatening impaired kidney histology or function (1). Non-compliance with immunosuppressants seems to be a major factor influencing renal graft survival, but it is difficult to detect in clinical settings due to the absence of clear medical paradigms, difficult and imprecise diagnosis. Researchers from different countries show that non-adherence is common in renal transplant recipients and it has a great impact on late graft dysfunction and survival (2). The frequency and prevalence of non-compliance vary widely: some authors find it in 47.6% (3) and 66.7% (4), respectively, whereas others find frequency of non-compliance just in 2% (5) of kidney transplant recipients, and prevalence of non-compliance in 1.4% (6).

The impact of non-adherence on transplant failure differs between studies. There are authors reporting about 78.6% of transplant failures in non-adherent groups from a total number of transplant failures (5) as well as 31.4 (1.8–551.8) odds of transplant failure in non-adherent groups compared to the adherent groups (7). At the same time there are researchers who demonstrate lower number (7%) of transplant failures in non-adherent groups and with only 4.5 (0.7–26.7) odds of transplant failure in non-adherent groups in comparison with the adherent groups (95% confidence intervals) (8). The absence of simple and exact diagnostic criteria evidently elucidates such diversity of the results.

There are a number of ways to approach the diagnosis of non-compliance syndrome (therapeutic drug monitoring of blood levels, pharmaceutical monitoring, event-related, physical examination and third party observation by parents, friends, spouse etc.), however, the only certainty comes from direct patient admission of non-adherence to the prescribed immunosuppressive drugs (1).

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The main objectives of our study were as follows: to compare the different compliance detection methods, to identify the prevalence of non-compliance, to verify factors associated with this condition, as well as to assess the long-term impact of non-adherence on graft and patient survival after renal transplantation.

MATERIALS AND METHODS

The study included 197 patients undergoing renal transplantation at the Latvian Transplantation Centre between January 2000 and June 2003, in a retrospective database analysis, having at least 36 months of follow-up, 171 first transplantations (86.8%) and 26 retransplantations (13.2%), of whom 117 (59.4%) were men and 80 (40.6%) were women aged 48.4 ± 14.6 (range 10–76). Two patients received kidney transplants from living related donors; the others received theirs from cadaver donors (Table 1). The PRA > 10% was noted in 8.4% of patients.

The diagnosis of non-compliance was based on patient self-admission to having discontinued the immunosuppressive drugs as the cause of graft dysfunction (self-report by questionnaires).

Table 1. **Demographic characteristics of all 197 participants and patients divided by compliance; numbers are frequency (percent), or average (± standard deviation)**

	All patients (n = 197)	Non-compliant patients (n = 16)	Compliant patients (n = 181)	p value[a]
Number	197	16 (8.1%)	181 (91.9%)	
Males	117 (59.4%)	9 (56.3%)	108 (59.7%)	NS
Cause of end-stage kidney disease				
GN	101 (51.3%)	9 (56.3%)	92 (50.8%)	NS
DM	26 (13.2%)	1 (6.2%)	25 (13.8%)	NS[c]
IN	22 (11.2%)	1 (6.2%)	21 (11.6%)	NS[c]
HTN	17 (8.6%)	1 (6.2%)	16 (8.8%)	NS[c]
PKD	21 (10.7%)	1 (6.2%)	20 (11.0%)	NS[c]
Other	10 (5%)	3 (18.9%)	7 (4.0%)	<0.0001[c]
Age at transplant years	43.7 ± 14.6	35.3 ± 13.8	44.5 ± 14.5	0.016[b]
Young <20 years old	6 (3.0%)	0 (0%)	6 (3.3%)	NS[c]
Primary graft	170 (86.3%)	1 (6.2%)	26 (14.4%)	NS[c]
Living related graft	2 (1%)	0 (0%)	2 (1.1%)	NS[c]
Time on waiting list before transplantation years	1.37 ± 1.15	1.60 ± 1.42	1.35 ± 1.13	NS[b]

Note. GN – chronic glomerulonephritis, DM – diabetes mellitus (type I and II), IN – interstitial nephritis, HTN – hypertensive nephropathy, PKD – polycystic kidney disease; [a] Comparisons between groups by chi-squared test unless otherwise noted; [b] Two-sample t test; [c] Fisher exact test, two-tailed.

Table 2. **Immunosuppressive regimens of all 197 patients and patients divided by compliance group**

Immunosuppression	Immunosuppression (%) in all patients (n = 197)	Immunosuppression (%) in non-compliant patients (n = 16)	Immunosuppression (%) in compliant patients (n = 181)	p value[a]
Triple immunosuppression	**138 (70.1%)**	**12 (75%)**	**126 (69.6%)**	**NS**
CyA + MMF + P	55 (27.9%)	8 (50.0%)	47 (26.0%)	0.029
CyA + Aza + P	81 (41.2%)	4 (25.0%)	77 (42.5%)	NS[b]
SRL + MMF + P	1 (0.5%)	0	1 (0.6%)	NS[b]
SRL + Aza + P	1 (0.5%)	0	1 (0.6%)	NS[b]
Double immunosuppression	**58 (29.4%)**	**4 (25%)**	**54 (29.8%)**	**NS[b]**
CyA + MMF	18 (9.2%)	0	18 (10.0%)	NS[b]
CyA + Aza	15 (7.6%)	1 (6.3%)	14 (7.7%)	NS[b]
CyA + P	17 (8.6%)	3 (18.8%)	14 (7.7%)	NS[b]
MMF + P	7 (3.5%)	0	7 (3.9%)	NS[b]
SRL + P	1 (0.5%)	0	1 (0.6%)	NS[b]
Single immunosuppression	**1 (0.5%)**	**0**	**1 (0.6%)**	**NS[b]**
CyA	1 (0.5%)	0	1 (0.6%)	NS[b]

Note. CyA – cyclosporin A, MMF – mycophenolate mofetil, P – prednisolone, Aza – azathioprine, SRL – sirolimus; [a] Comparisons between groups by chi-squared test unless otherwise noted; [b] Fisher exact test, two-tailed.

A variety of immunosuppressive drug protocols has been used in our transplant unit over time. The following drugs were used in different combinations: prednisolone, cyclosporine A, azathioprine, mycofenolate mofetil, sirolimus. The ten basic (triple, dual or mono therapy) maintenance immunosuppressive regimens (induction treatment data are not presented) were identified (Table 2).

Acute and chronic rejection was diagnosed on the basis of clinical evidence and mainly confirmed by a percutaneous biopsy. The typical histological features were graded by the pathologist according to the Banff 1997 scheme.

Chronic graft dysfunction and failure were assessed by creatinine clearance, calculated by using the Cockroft-Gault formula, as well as confirmed by graft biopsy or at nephrectomy.

Participants were asked to sign a consent form to be returned with the questionnaire, and the study was approved by the local ethics committee. All of the clinical information is stored in an electronic database, which was the primary source of information for this study.

All immunosuppressive medication, as well as erythropoetin and "statins" are fully covered by the compulsory health insurance to all the transplant recipients in Latvia, and every patient receives it free of charge. Out-patient clinical visits and laboratory investigation are partially covered by the health insurance and patients have to pay the so-called "co-payment", approximately 3 € for each visit, including laboratory investigations.

Patients were divided into two groups (compliant and non-compliant patients) to identify non-compliant patients according to demographics and specifically related to the transplant parameters, as well as to detect the impact of non-adherence on long-term clinical outcomes of renal transplant recipients.

Statistical methods

Unpaired Student's t-test was used for comparisons involving continuous variables when normal distribution was confirmed by the Kolmogorov-Smirnov (KS) test. If the KS test showed significant ($p < 0.05$) non-normal distribution, the non-parametric Mann-Whitney U test was used to compare continuous variables. The chi-square test was used for comparisons involving categorical variables, except when the expected cell size fell below 5, in which case the Fisher exact probability test was used. Pearson correlation coefficients were used to assess the correlation between three different compliance detection methods. Kaplan-Meier analysis was used to estimate overall patient and graft survival.

Multivariate linear forward stepwise regression analysis was performed to determine the independent variables predicting non-compliance after renal transplantation. Variables which showed significance in the initial screening by the Mann-Whitney or the chi-square test were implemented. Results were presented as standardised regression coefficients β. P values less than 0.05 were considered significant. All the analyses were performed using SPSS v-10 statistical package (Chicago, IL, USA).

RESULTS

There were 197 eligible patients with complete 3-year follow-up information available and the data from all four non-compliance detection surveys.

Prevalence of non-compliance

Sixteen out of 197 patients (8.1%) admitted being non-compliant to the immunosuppressive medication regimen (missed taking immunosuppressive medication as requested at least once a month).

Characteristics of compliant and non-compliant patients

The main baseline characteristics of all the patients and patients divided by compliance groups are shown in Table 1. The two cohorts were similar concerning demographics, clinical characteristics and the main underlying diseases, with the exception of patients' age. Non-compliant patients were younger at the time of transplantation ($p = 0.016$). Difference in terms of rare causes of kidney failure (mentioned as other causes) seems to be unexplainable and of minor importance.

More than 70% of patients were taking triple immunosuppression (Table 2). The rest (29.4%), except for one patient, were maintained on double immunosuppression. Altogether, cyclosporin A-based immunosuppressive regimens tended to consist of the highest pill amount (Table 3).

Table 3. **Immunosuppressive medication pills taken daily by different immunosuppressive regimens (mean ± SD)**

Immunosuppression	Number of immunosuppressive pills per protocol
Triple immunosuppression	
CyA + MMF + P	7.9 ± 1.8
CyA + Aza + P	6.4 ± 1.5
SRL + MMF + P	5
SRL + Aza + P	6
Double immunosuppression	
CyA + MMF	6.9 ± 2.0
CyA + Aza	6.1 ± 1.5
CyA + P	4.8 ± 1.8
MMF + P	3.8 ± 1.6
SRL + P	3
Single immunosuppression	
CyA	4

Note. CyA – cyclosporin A, MMF – mycophenolate mofetil, P – prednisolone, Aza – azathioprine, SRL – sirolimus.

Just one medication regimen – triple immunosuppression consisting of cyslosporin A + mycophenolate mofetil + prednisolone (the regimen with the highest number of pills per day) – revealed significant difference between groups: a greater proportion of non-compliant patients were taking daily triple immunosuppression with the highest number of pills ($p = 0.029$).

Table 4. **Graft and patient outcomes of all 197 participants and patients divided by compliance group**

Event (%)	All patients (n = 197)	Non-compliant patients (n = 16)	Compliant patients (n = 181)	OR for event in non-compliant patients compared with the compliant patients (95%CI)	p value[a]
Acute rejection	53 (26.9%)	8 (50%)	45 (24.9%)	3.02 (1.07–8.52)	0.035
Chronic graft dysfunction	45 (22.8%)	7 (43.8%)	38 (21%)	2.93 (1.02–8.37)	0.045
Graft failure including all causes of failure	80 (40.6%)	12 (75%)	68 (37.6%)	4.99 (1.55–16.08)	0.006
Graft failure excluding death with functioning graft (return to dialysis)	53 (26.9%)	9 (56.2%)	44 (24.4%)	4.00 (1.41–11.38)	0.009
Patient's death	45 (22.8%)	5 (31.2%)	40 (22.1%)	1.60 (0.53–4.88)	NS
Death with functioning graft	27 (13.7%)	3 (18.6%)	24 (13.3%)	1.51 (0.40–5.69)	NS[b]

Note. [a] Comparisons between groups by chi-squared test unless otherwise noted; [b] Fisher exact test, two-tailed.

Patient and graft outcomes of compliant and non-compliant patients

All the patients were followed for 3 years starting from the time of transplantation. Clinical graft and patient outcomes between non-compliant and compliant patients are compared in Table 4. Acute graft rejection, as well as chronic graft dysfunction was more frequent in non-compliant patients. Graft failure, including either all causes of graft failure or graft failure excluding death with functioning graft (i. e. return to dialysis), were also more common in non-compliant patients. Our results showed that 15.1% of all acute rejections, 15.6% of chronic graft dysfunction, 15.0% of graft failure including all the causes of failure, and even a higher percentage (17.0%) of graft failure, excluding patients who died with the functioning graft, were associated with non-compliance (number of events in the non-compliant group / total number of events (%). However, we did not find any difference in patient outcomes (patient's death and death with functioning graft) between non-compliant and compliant patients. Increased odds ratios for different graft and patient outcomes in non-compliant patients are shown in Table 4.

The one and three year actuarial graft survival is shown in Fig. 1. Compliant patients demonstrated 78.5% one-year graft survival rate, and 66.3%, a three-year graft survival rate, while in non-compliant patients, the one-year graft survival rate was 68.8%, while the three-year graft survival rate was 43.7% ($p < 0.01$). Patients' deaths including those who died with the functioning graft and those who returned to dialysis were similar in both groups. The one and three year actuarial patient survival rates in non-compliant and compliant group also showed no advantages for compliant patients (Fig. 2).

Predicting non-compliance

Results of a multiple linear regression revealed that after adjusting for patient's sex and diabetic status, two variables were independently associated with becoming non-compliant: age at the time of transplantation and triple immunosuppressive regimen (CyA + MMF + P) containing the largest amount of pills. A negative correlation existed between non-compliance of patients after renal transplantation and the patients' age at the time of transplantation, i. e. younger patients were more likely to be non-compliant. Standardized regression coefficient β for being non-compliant was −0.172 ($p = 0.016$) for this

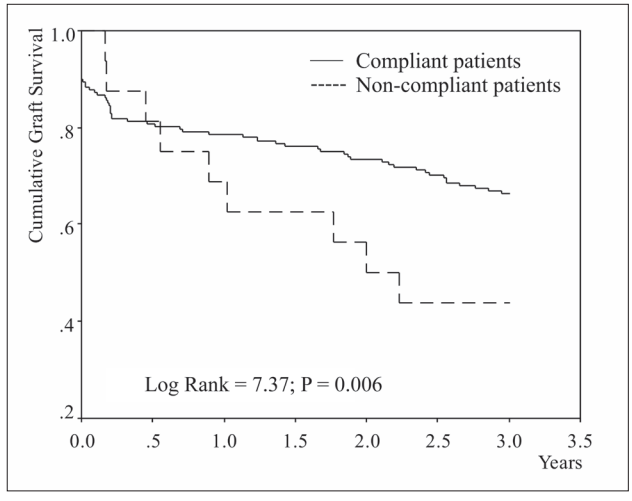

Fig. 1. Kaplan-Meier estimates of 3-year graft survival among compliant (n = 181) and non-compliant (n = 16) patients (Log Rank = 7.37; p = 0.0066)

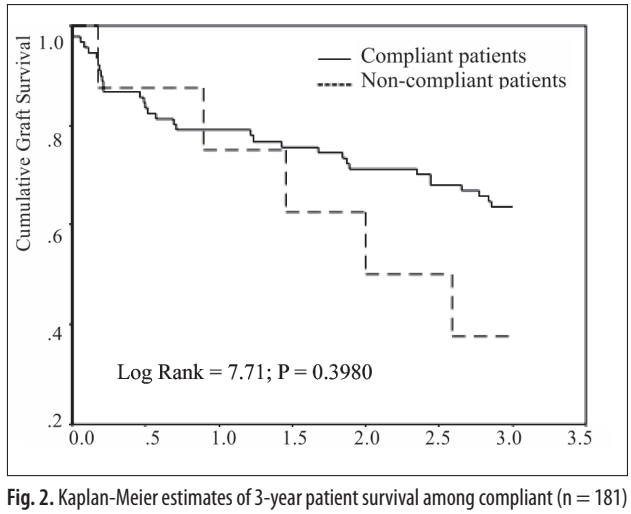

Fig. 2. Kaplan-Meier estimates of 3-year patient survival among compliant (n = 181) and non-compliant (n = 16) patients (Log Rank = 0.71; p = 0.3980)

variable. On the other hand, we found a positive correlation between non-compliance and immunosuppressive medication regimen which contained the most immunosuppressive pills. Standardized regression coefficient β for being non-compliant in patients with the above mentioned immunosuppressive schedule was 0.148 ($p = 0.046$) for this variable.

DISCUSSSION

Kidney loss in the first ten years after transplantation still remains a significant problem despite advances in treating acute and chronic rejection and development of new immunosuppressive protocols. It was found that non-compliance was one of the leading causes of graft loss after an initial period of graft loss due to rejection or infection (9–11).

Our results showed 8.1% of non-compliance by the self-admission method. We employed the results from patients' self-report questionnaires because we found it to be one of the most precise and ethical ways to approach the diagnosis of non-compliance.

In comparison to the published data (5, 12), the prevalence of non-compliance in our study was rather low, but in the systematic review, presented by Butler et al., which included 36 studies of non-compliance after renal transplantation, the authors reported the median frequency of non-adherence to be 15% (2), which was consistent with our results. It should be pointed out, that there is no perfect method elaborated for the diagnostics of non-compliance. Even the so-called "self admission" method, which has been recognized as quite precise, possesses an essential fault: patients unwillingly avow their non-compliance, and for that reason this method may uncover only major non-compliance, the situation when a patient dramatically violates the immunosuppressive regime followed by a rejection episode and graft loss as a consequence (13). Thus, the frequency and impact of non-compliance on renal transplant outcomes could be underestimated. However, on the other hand, such a comparatively low prevalence of non-compliance could be interpreted with free-of-charge transplantation and immunosuppressive medications given to all the transplant patients in Latvia. The average duration of hospital stay (28 days) after renal transplantation is considered to be quite sufficient to acquire "co-existence with graft". But recently it seems more and more, that awareness of free access to medications after transplantation causes the so-called "self-care behaviour" (14) deficiency, thus stimulating consumer's morality and non-compliance.

While analysing and comparing the demographic and transplant-related data obtained between compliant and non-compliant recipients, it was found that non-compliant patients were remarkably younger in comparison to the compliant recipients. However, it is necessary to point out that there were no non-compliant recipients among the patients under the age of 20 (all the children were included). These findings vastly differ from the information available on children and young people as a potential risk factor of non-compliance (1) as well as on remarkably higher non-compliance of children and teenagers in comparison to adult people (15, 16).

An especially typical situation in renal transplantation of Latvia appeared while analysing recipient's mean time on the waiting list, which turned out to be short for both non-compliant, as well as compliant recipients (no longer than two years). Taking into consideration, that the waiting time on the waiting list was so short, the higher prevalence of non-compliance should be expected due to the fact, that patients frequently have undergone transplants without being psychologically prepared, but we did not uncover a link between a shorter waiting time and a higher non-compliance in the post transplantation period in the present study.

Having analysed 10 maintenance immunosuppressive therapy protocols, it was stated that the triple immunosuppressive protocol alone based on cyclosporine A, mycofenolate mofetil and prednisolone was associated with a statistically significant higher percentage of non-compliance as compared to all the other immunosuppressive regimens due to a greater number of pills per day. Very promising, both from a clinical as well as from the compliance point of view seem to be the double immunosuppressive protocols based either on mycofenolate mofetil or on sirolimus. Combination of sirolimus with prednisolone or with small doses of mycofenolate mofetil could be considered to be preferable, because, as far as we know, sirolimus has been used once a day. It remarkably promotes adherence with immunosuppressive medications, as the frequency of medications dosing is also a significant risk factor for noncompliant behaviour after transplantation (1), and such simultaneous, double, sirolimus-based immunosuppressive protocol can provide excellent long-term graft function (17).

During the studies of the impact of non-compliance on the graft function and survival, we disclosed a significantly higher rate of acute rejection (50%), as well as chronic graft dysfunction (43.8%) in the noncompliant recipient group in comparison to the compliant group (24.95% and 21%, respectively). Also the graft failure including all the causes of failure and graft failure excluding death with functioning graft (return to dialysis) was considerably frequent in the noncompliant group, 75% and 56.2%, respectively. The three-year actuarial graft survival rate in the compliant group was 66.3% while in noncompliant one it was 43.7%. These findings are consistent with the previously reported studies (7, 8, 18, 19) and confirmed the negative impact of non-adherence on renal graft function, as well as on late graft survival.

We did not find any difference in patient outcomes between non-compliant and compliant patients. Patients' deaths, including those who died with functioning graft and those who returned to dialysis, were similar in both groups.

In conclusion we agree with Butler and his colleagues, that detection of non-adherence should not be the main goal of future research; more importantly, there is a necessity to understand the factors that lead to non-adherence (2).

The regimens with the lesser number of pills, especially immunosuppression based on sirolimus and mycofenolate mofetil, could be one of the solutions for the promotion of patients' compliance in the late post-transplantation period.

At the same time, more careful patient's psychosocial evaluation presented to physicians is advisable, because very often patients who have been indicated and accepted to kidney transplantation could manifest their non-compliance already during dialysis.

Taking into consideration the enormous impact of non-compliance on graft function and lifetime, next step of our studies will pay particular attention to the economic implications of non-adherence in the late period after renal transplantation.

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References

1. Chapman JR. Compliance: the patient, the doctor, and the medication? Transplantation 2004; 15: 782–6.
2. Butler JA, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. Transplantation 2004; 15: 769–89.
3. Douglas S, Blixen C, Bartucci MR. Relationship between pretransplant noncompliance and posttransplant outcomes in renal transplant recipients. J Transpl Coord 1996; 6: 53–8.
4. Chisholm MA, Vollenweider LJ, Mulloy LL et al. Renal transplant patient compliance with free immunosuppressive medications. Transplantation 2000; 70: 1240–4.
5. Kiley DJ, Lam CS, Pollak R. A study of treatment compliance following kidney transplantation. Transplantation 1993; 55: 51–6.
6. Fernandez Lucas MF, Sanchez JL, Miranda B, Matesanz R. Adhesion to the treatment in renal transplant recipients. A Spanish multicentric trial. Nefrologia 1998; 18: 316–25.
7. Butkus DE, Dottes AL, Meydrech EF, Raju SS. Racial differences in the survival of cadaveric renal allografts. Overriding effects of HLA matching and socioeconomic factors. New Engl J Med 1992; 327: 840–5.
8. Kalil RS, Heim-Duthoy KL, Kasiske BL. Patients with a low income have reduced renal allograft survival. Am J Kidney Dis 1992; 20: 63–9.
9. Didlake RH, Dreyfus K, Kerman RH, VanBuren CT, Kahan BD. Patient noncompliance: A major cause of late graft failure in cyclosporine-treated renal transplants. Transplant Proc 1988; 20: 63–9.
10. Rovelli M, Palmeri D, Vossler E, Bartus S, Hull D, Schweizer R. Noncompliance in organ transplant recipients. Transplant Proc 1989; 21: 833–4.
11. Schweitzer EJ, Matas AJ, Gillingham KJ et al. Causes of renal allograft loss. Ann Surg 1991; 214: 679–88.
12. Douglas S, Blixen C, Bartucci MR. Relationship between pretransplant noncompliance and posttransplant outcomes in renal transplant recipients. J Transpl Coord 1996; 6: 53–8.
13. Rosenberger J, Geckova AM, van Dijk JP et al. Prevalence and characteristics of noncompliant behaviour and its risk factors in kidney transplant recipients. Transplant Int 2005; 18: 1072–8.
14. Gordon EJ, Prohaska T, Siminoff LA, Minich PJ, Sehgal AR. Can focusing on self-care reduce disparities in kidney transplantation outcomes. Am J Kidney Dis 2005; 45: 935–40.
15. Cecka JM, Gjerston DW, Terasaki PI. Pediatric renal transplantation: a review of the UNOS data. United Network for Organ Sharing. Pediatr Transplant 1997; 1: 55–64.
16. Rianthavorn P, Ettenger RB, Malekzadeh M, Marik JL, Struber M. Noncompliance with immunosuppressive medications in pediatric and adolescent patients receiving solid-organ transplants. Transplantation 2004; 77: 778–82.
17. Mota A, Arias M, Taskinen EI, Paavonen T et al. Sirolimus-based therapy following early cyclosporine withdrawal provides significantly improved renal histology and function at 3 years. Am J Transplant 2004; 4: 953–61.
18. Schweitzer RT, Rovelli M, Palmeri D, Vossler E, Hull D, Bartus S. Noncompliance in organ transplant recipients. Transplantation 1990; 49: 374–7.
19. Michelon TF, Piovesan F, Pozza R et al. Noncompliance as the cause of renal graft loss. Transplant Proc 2002; 34: 2768–70.