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Long-term renal allograft function under maintenance immunosuppression with cyclosporin A or azathioprine

A single center, five-year follow-up study

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Abstract. In order to evaluate long-term renal graft function, 149 cyclosporin A and prednisolone (CyA/P)-treated renal transplant recipients were compared with 119 azathioprine and prednisolone (Aza/P)-treated patients. Only patients who had a functioning graft for at least 1 year and who were maintained on their initial immunosuppressive protocol were included. The minimum follow-up period was 4 years. Renal graft function was estimated by yearly determinations of serum creatinine and creatinine clearance. The CyA/P-treated patients had a significantly higher serum creatinine and a significantly lower creatinine clearance at every point in time post-transplantation than Aza/P-treated patients ($P < 0.001$). The evolution of renal graft function, as reflected in the line of regression for serum creatinine and creatinine clearance versus time, was estimated for each individual patient. There was an almost stable renal function, as assessed by the median of the slopes of the regression line for serum creatinine versus time in both groups. The median increase in serum creatinine was only 1.4 μmol/l per year for Aza/P-treated patients and 2.4 μmol/l per year for CyA/P-treated patients (difference NS). The median decline in creatinine clearance was 2.18 ml/min per 1.73 m^2/year in the Aza/P group and 1.07 ml/min per 1.73 m^2/year in the CyA/P group ($P = 0.05$). In patients with a functioning graft for at least 5 years, creatinine clearance remained unchanged in both groups during the study period. In conclusion, renal graft function, as assessed by measurements of serum creatinine and creatinine clearance, remained essentially unchanged for at least 5 years after transplantation, regardless of the immunosuppressive protocol used. Thus, these data do not indicate a progression with time of the nephrotoxicity observed in CyA-treated patients.

Key words: Long-term results, kidney transplantation – Cyclosporin A, long-term results, kidney transplantation – Azathioprine, long-term results, kidney transplantation

In kidney transplantation there is a growing interest in the long-term function of renal allografts under maintenance immunosuppression with the nephrotoxic drug cyclosporin A (CyA). As yet, reports are somewhat contradictory, suggesting either chronic and progressive deterioration of native, previously healthy kidneys in heart [15–17] and liver recipients [13] or stable function of native kidneys [5, 8] and of renal allografts [2, 6, 7, 19] over time. However, the previous studies in renal transplant recipients are not conclusive, due to short follow-up, small numbers of patients, and lack of a control group. Furthermore, serial determinations of serum creatinine, which formed the basis for evaluation of renal graft function in most of these studies may, in the long run, reflect a tendency rather than precisely describe the level or the dynamics of alterations in graft function [14, 21]. Multicenter reports may include additional sources of error, such as differences in laboratory methods (as is known for serum creatinine) [10] and in follow-up routines.

The aim of the present study was to describe the long-term evolution of renal allograft function as assessed by serial measurements of serum creatinine and creatinine clearance, with special reference to the maintenance immunosuppressive therapy. Thus, we retrospectively compared the renal graft function of 147 CyA/prednisolone (CyA/P)-treated patients with that of 119 azathioprine/prednisolone (Aza/P)-treated renal transplant recipients who maintained their original immunosuppressive protocols and who had a functioning graft for at least 1 year. The minimum follow-up was 4 years in all patients and 5 years in 78% of the patients.

Patients and methods

Out of a total of 412 consecutive adult kidney recipients transplanted between January 1977 and February 1985, 266 had a functioning graft for at least 1 year and were included in the present

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Table 1. Demographic data on the 119 patients treated with azathioprine and prednisolone (Aza/P) and on the 147 patients treated with cyclosporin and prednisolone (CyA/P)

Treatment group	Aza/P		CyA/P		Significance Aza/P vs CyA/P
Donor	LRD	CD	LRD	CD	
Number of patients	23	96	47	100	
Mean age ± SD (years)	26.3 ± 8.3	46.5 ± 12.8	31.0 ± 13.9	49.2 ± 13.7	NS
Sex: M:F	12:11	57:39	27:20	65:35	NS
Number of retransplants	1	28	5	19	NS
End-stage renal disease:					
Chronic glomerulonephritis	44%	42%	49%	45%	NS
Pyelonephritis	4%	17%	11%	10%	NS
Diabetes mellitus	22%	11%	9%	9%	NS
Polycystic kidney disease	0	16%	4%	9%	NS
Congenital disorders	13%	1%	6%	6%	NS
Other	17%	13%	21%	21%	NS
Pretransplant blood transfusions:					
0	0	2%	27%	20%	[a]
L1	100%	98%	73%	80%	[a]
Cold ischemia time (mean ± SD)	–	28h18min ± 7h58min	–	25h10min ± 5h15min	0.003
Donor age ± SD (years)	54.3 ± 11	40.0 ± 15.7	48.7 ± 11.3	43.7 ± 13.8	NS
Mismatches in HLA-A:	$n = 110$		$n = 147$		
0	8%	26%	10%	21%	NS
1	13%	41%	21%	26%	NS
2	0%	12%	0%	22%	NS
Mismatches in HLA-B:	$n = 110$		$n = 147$		
0	5%	28%	7%	7%	NS
1	15%	31%	24%	33%	NS
2	0%	21%	0%	29%	NS
Mismatches in HLA-DR:	$n = 47$		$n = 142$		
0	6%	66%	16%	23%	NS
1	2%	19%	16%	33%	NS
2	0%	7%	0%	12%	NS

[a] Pretransplant blood transfusions were given routinely to Aza/P-treated patients

study. Patients who were converted to combination therapy with CyA and azathioprine were excluded (i.e., a total of 13 azathioprine-treated and 9 CyA-treated patients). There were 213 recipients of a first transplant and 53 retransplanted recipients. Seventy patients received their graft from a living related donor (LRD) and 196 patients received a cadaveric donor (CD) allograft. The follow-up period ranged from 79 to 148 months for Aza/P-treated patients and from 50 to 108 months for CyA/P-treated patients. The demographic data of the patients are displayed in Table 1.

Aza/P group

This group included 119 patients who underwent renal transplantation in the period from 1977 to 1982 and who had a functioning graft for at least 1 year after transplantation. Maintenance immunosuppression consisted of azathioprine and prednisolone. Azathioprine, 3 mg/kg, was given orally immediately prior to transplantation. Postoperatively, a dose of 2 mg/kg per day or less was given if there was a low leukocyte count. At 1, 3, and 5 years after transplantation, the mean dose of azathioprine was 1.5 ± 0.8, 1.4 ± 0.7, and 1.4 ± 0.7 mg/kg per day, respectively.

Prednisolone was administered at an initial dose of 120 mg/day (40 mg/day to patients aged > 60 years) and tapered to 30–35 mg/day at 1 month postoperatively. A maintenance dose of 10 mg/day was reached at 18 months after transplantation. At 1, 3, and 5 years after transplantation the mean dose of prednisolone was 0.21 ± 0.06, 0.15 ± 0.03, and 0.15 ± 0.03 mg/kg per day, respectively.

Patients transplanted during 1977 also received 15–30 mg/kg per day antithymocyte globulin (AHLG, Behringwerke, Marburg, FRG; $n = 23$), i.v. for 3 weeks after transplantation. Patients transplanted after 1980 received an additional 1 mg/kg per day rabbit antithymocyte globulin (RATG, Stanford, Calif., USA; $n = 49$) i.m. for 14 days after transplantation.

Acute rejection episodes were treated with 0.5 g methylprednisolone for 5 consecutive days (patients transplanted from 1977 to 1979) or 0.5 g the first day and 0.25 g daily for 4 days (patients transplanted after 1979).

CyA/P group

A total of 147 patients, transplanted from 1980 to 1985, had a functioning graft for at least 1 year and were treated with CyA/P according to a standard protocol. During the first 2 days, 10–15 mg/kg CyA was given i.v. on the day of transplantation and 7.5 mg/kg on the first postoperative day. Starting on day 2, 15 mg/kg CyA was given orally, divided in two daily doses. The dose was reduced to 13 mg/kg per day after 2 weeks, to 11 mg/kg per day after 1 month, and to 9 mg/kg per day after 2 months. Plasma or whole blood levels of CyA were monitored and the dose was lowered when the concentrations became too high and/or clinical signs of CyA toxicity appeared. Analysis was performed with polyclonal RIA (Sandoz, Basel, Switzerland), aiming at a whole blood trough level of 400–800 ng/ml during the first month, and decreasing to 150–400 ng/ml after 6 months. At 1, 3,

Table 2. Clinical results

Treatment group	Aza/P		CyA/P		Significance Aza/P vs CyA/P	
	LRD	CD	LRD	CD		
Patients	$n = 23$	$n = 96$	$n = 47$	$n = 100$	LRD	CD
Number of acute rejections:						
0	22%	42%	62%	53%		
≥ 1	78%	58%	38%	47%	0.004	NS
Cause of graft loss:	$n = 13$	$n = 48$	$n = 12$	$n = 35$		
Rejection	9 (69%)	24 (50%)	5 (42%)	16 (46%)	NS	NS
Death with functioning graft	3 (23%)	20 (42%)	5 (42%)	17 (49%)	NS	NS
Other	1 (8%)	4 (8%)	2 (16%)	2 (5%)	NS	NS
Cause of death (functioning and nonfunctioning grafts):	$n = 1$	$n = 27$	$n = 6$	$n = 19$		
Cardiovascular	1	12 (45%)	1 (17%)	10 (52%)	NS	NS
Infection	0	3 (11%)	0	3 (16%)	NS	NS
Malignancy	0	3 (11%)	0	0	NS	NS
Other	0	9 (33%)	5 (83%)	6 (32%)	NS	NS

and 5 years after transplantation, the mean dosage of CyA was 4.6 ± 2.7, 3.4 ± 2.1, and 3.0 ± 1.8 mg/kg per day, respectively.

Prednisolone was administered orally at a dose of 100 mg/day on the day of transplantation and was thereafter tapered by 10 mg/day until day 9, when a dose of 20 mg/day was given. A maintenance dose of 10 mg/day was reached at 3 months after transplantation. At 1, 3, and 5 years after transplantation, the mean dose of prednisolone was 0.16 ± 0.09, 0.14 ± 0.06, and 0.13 ± 0.06 mg/kg per day, respectively.

Acute rejection episodes were treated with methylprednisolone, 0.5 g the first day and then 0.25 g daily for 3 days.

Routine follow-up

Starting the second year post-transplantation, outpatient examinations were performed at least twice yearly. Yearly determinations of weight, blood pressure, daily urinary output, and concentration of creatinine in serum and in 24-h urine samples for determination of the endogenous creatinine clearance (corrected to the standard body surface area) were collected. A total of 1347 determinations of serum creatinine (mean 5.0 per patient) and a total of 1153 determinations of creatinine clearance (mean 4.3 per patient) were studied. All analyses of creatinine in serum and urine were performed using the enzymic Jaffé method at the Department of Clinical Chemistry at our hospital [12].

In the case of deteriorating graft function, a core biopsy of the renal transplant was usually performed, and acute rejection episodes were treated as described above. Medical antihypertensive treatment was administered or altered when the blood pressure exceeded a diastolic limit of 95 mm Hg in an adult patient.

Statistical methods

For patient data collection and analysis, the MEDLOG clinical data management system (Information Analysis, Mountain View, Calif., USA) was used. Student's *t*-test was used for parametric analysis and the chi-square test, the Wilcoxon signed rank test, and the Mann-Whitney U-test were used for nonparametric analysis. Comparison of graft and patient survival between the groups was calculated according to the Mantel-Haenszel log rank test. Slopes of linear regression of serum creatinine and creatinine clearance were determined individually for each patient using the method of least squares. Multiple linear regression was performed according to Armitage [1]. The confidence intervals were calculated by the MINITA B program (Statistics Department, Pennsylvania State University, Pa., USA).

Results

Demographic comparison

There were no significant differences between the patient groups regarding age or sex distribution, number of retransplantations, diagnosis, donor age, or source or proportion of HLA-A- or B-mismatches (Table 1). DR-typing was performed in only 39% of the transplantations in the Aza/P group. Cold ischemia times were significantly shorter in the CyA/P group ($P = 0.003$), and preoperative blood transfusions were not given routinely under CyA treatment.

Graft and patient survival

There was no significant difference in successive graft loss rate between the two groups (log rank test). Thus, the patient and graft survival rates at 5 years after transplantation were 81.5% and 64.7%, respectively, in the Aza/P group and 86.4% and 71.0% in the CyA/P group (NS). However, when graft losses during the first year after transplantation were taken into account, a large difference was found in graft survival between Aza/P-treated and CyA/P-treated patients. During that time period, the 1- and 5-year graft survival rates were 53.3% and 34.7% in Aza/P-treated patients ($n = 219$). The corresponding figures in CyA/P-treated patients ($n = 193$) were 74.6% and 52.8%; $P < 0.01$.

Clinical course

Acute rejection episodes occurred more frequently in Aza/P-treated LRD recipients than in CyA/P-treated LRD recipients (78% versus 38%; $P = 0.004$; Table 2). However, there was no significant difference in the occurrence of acute rejection episodes between Aza/P-treated and CyA/P-treated CD recipients ($P = 0.15$).

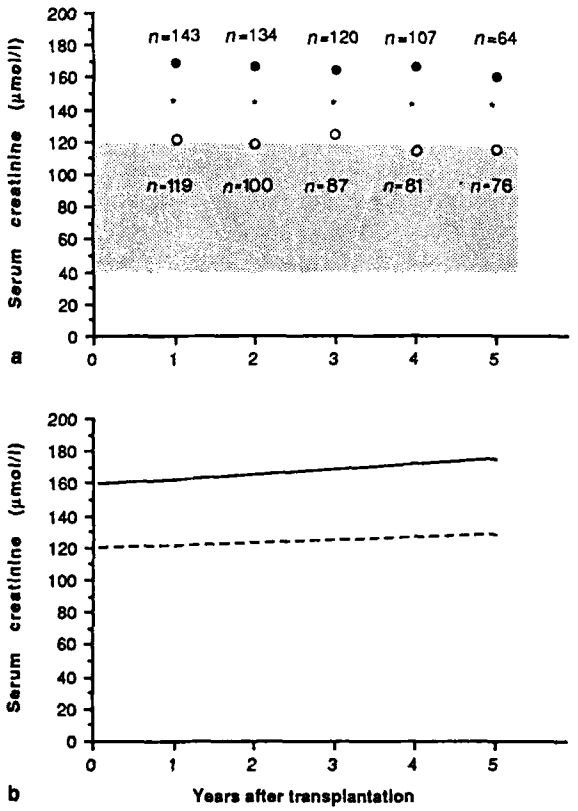

Fig. 1. **a** Median serum creatinine levels at 1–5 years after transplantation. ○ Aza/P-treated patients; ● CyA/P-treated patients. * $P < 0.001$, Mann-Whitney U-test. **b** Median intercepts and slopes for the individual lines of regression. --- Aza/P-treated patients; — CyA/P-treated patients

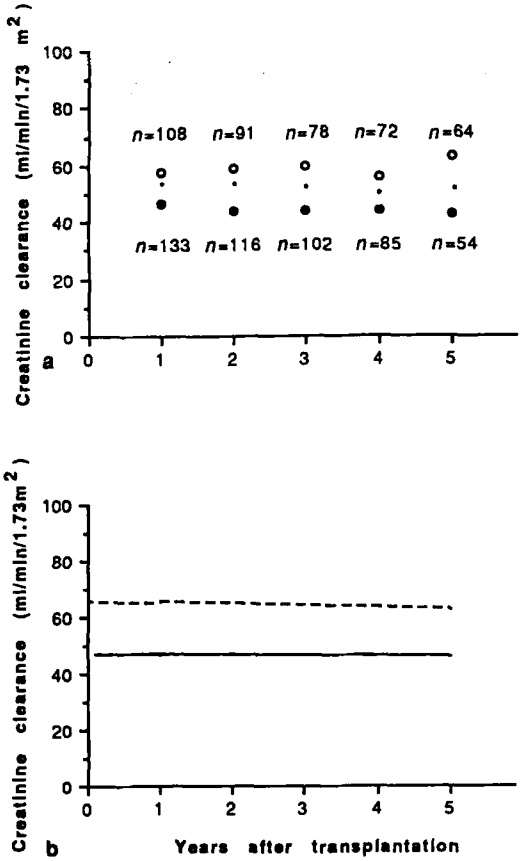

Fig. 2. **a** Median *creatinine clearance* levels at 1–5 years after transplantation. ○ Aza/P-treated patients; ● CyA/P-treated patients. * $P < 0.01$, Student's *t*-test. **b** Median intercepts and slopes for the individual lines of regression. --- Aza/P-treated patients; — CyA/P-treated patients

Chronic rejection and death with a functioning graft were almost equally common as causes of graft loss in both patient groups (Table 2). Of the Aza/P-treated patients, 28 died compared with 25 in the CyA/P group (NS; Table 2). There was no difference in the cause of death between the groups, cardiovascular disease being the major cause of death in both.

Graft function in Aza/P-treated versus CyA/P-treated patients

Aza/P-treated patients had an almost normal median serum creatinine level from 1 to 5 years after transplantation (median ranging from 120 to 127 μmol/l; Fig. 1). In the CyA/P group, serum creatinine was significantly higher than in the Aza/P group at every point in time (median difference 33 μmol/l; 95% confidence interval 17.0–54.0 μmol/l; $P < 0.001$, Mann-Whitney U-test).

As for the creatinine clearance, the differences between the Aza/P and the CyA/P groups were statistically significant (median difference 16 ml/min per 1.73 m^2; confidence interval 6.0–26.0 ml/min per 1.73 m^2; $P < 0.01$ at 4 years and $P < 0.001$ at 1, 2, 3, and 5 years; Fig. 2).

The evolution of renal graft function, as reflected in the line of regression versus time, was estimated for each individual patient. There was no difference between the Aza/P and the CyA/P groups in the median slopes of the individual lines of regression versus time of serum creatinine (Figs. 1 b, 2 b; Table 3). The decline in creatinine clearance was not different from zero in CyA/P-treated patients and was extremely slow; however, it tended to be higher in Aza/P-treated patients, who had a decline in clearance of 2.18 ml/min per 1.73 m^2 year ($P = 0.05$; Table 3).

With regard to patients with a functioning graft for at least 5 years, the serum creatinine and creatinine clearance were stable in both groups during the observation period (Table 3).

Graft function in patients with subsequent graft loss

A separate analysis was performed in order to study whether a potential difference in graft function between the groups was more pronounced in patients who lost their graft. Patients who died with a functioning graft were not included in this analysis. As indicated in Table 3, there was no difference in the rate of decline of serum creatinine between the two groups. However, there was a tendency to faster decline in creatinine clearance in Aza/P-treated patients than in CyA/P-treated patients ($P = 0.06$). Figure 3 shows the individual serum creatinine versus time curves in patients with subsequent graft loss.

Table 3. Median slopes of the individual lines of regression versus time of serum creatinine and creatinine clearance in all Aza/P-treated and CyA/P-treated patients, as well as in the subgroups of patients with grafts functioning for at least 5 years and in patients with subsequent graft loss except for deaths with functioning grafts. The statistical comparisons between the groups were performed with the Mann-Whitney U-test

Variable	Aza/P group	CyA/P group	*P*-value
Serum creatinine (μmol/l per year)			
All patients	1.40	2.41	0.27
Patients with graft function for at least 5 years	0.33	0.10[a]	0.41
Patients with subsequent graft loss	40.3	31.1	0.77
Creatinine clearance (ml/min per 1.73 m^2/year)			
All patients	−2.18	−1.07[a]	0.051
Patients with graft function for at least 5 years	−0.97[a]	−1.18[a]	0.47
Patients with subsequent graft loss	−8.1	−4.4[a]	0.060

[a] Value not significantly different from zero

Hypertension

Blood pressure regulation is closely related to renal function. Moreover, hypertension is a well-known side effect of CyA treatment. Mean arterial blood pressure was higher in CyA/P-treated patients than in Aza/P-treated patients at 1 year post-transplantation (111 ± 13 mm Hg compared to 106 ± 15 mm Hg; $P < 0.05$). However, there was no difference at 3 and 5 years post-transplantation. One year after transplantation, an equal proportion of about 60% of the patients in both groups received antihypertensive treatment (Fig. 4). This percentage did not change in the Aza/P-treated patients. However, in the CyA/P group, we found a continously and significantly increasing proportion of patients requiring medical treatment for elevated blood pressure (Fig. 4).

Graft function and demographic and post-transplantation parameters

The possible influence of different variables on the evolution of serum creatinine and creatinine clearance after transplantation was studied in CyA/P-treated patients with remaining graft function at 5 years after transplantation by means of a multivariate linear regression analysis. The evolution of serum creatinine or creatinine clearance was not influenced by any of the parameters studied, i.e., recipient or donor age, sex, number of transplants, LRD versus CD recipients, number of pretransplant blood transfusions, cold ischemia time, number of HLA-A, -B and -DR-mismatches, or occurrence of acute rejection episodes.

Discussion

The question of whether there is a chronic and progressive decline in renal graft function under maintenance immunosuppression with CyA is presently being debated [2, 6, 7, 19]. The reports are somewhat contradictory, due to differences in the clinical situation, in the CyA dosage regimen, and in the parameters used for evaluation of renal function.

In the present single center analysis, the demographic factors were similar in the Aza/P and in the CyA/P groups. Interestingly, we failed to find any influence of the immunosuppressive regimen on the rate of graft losses more than 1 year after transplantation. This was in agreement with the studies of Cook and of Terasaki et al. [3, 24], as well as with recent Scandinavian data [11]. However, since CyA is nephrotoxic, it was interesting to study the possible influence of time on renal function in CyA-treated patients, with azathioprine-treated patients serving as historical controls.

We are well aware that the observation of kidney function by means of serum creatinine or creatinine clearance is not always a reliable measure of the glomerular filtra-

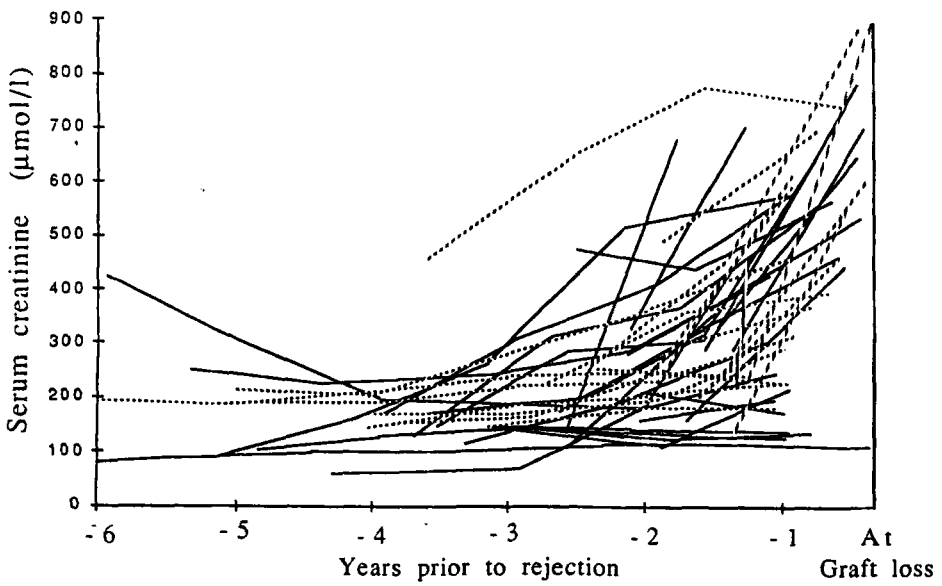

Fig. 3. Yearly individual *serum creatinine* versus time curves in Aza/P-treated patients *(solid lines)* and CyA/P-treated patients *(broken lines)* who subsequently lost their grafts during the observation period. Patients who died with functioning grafts were excluded

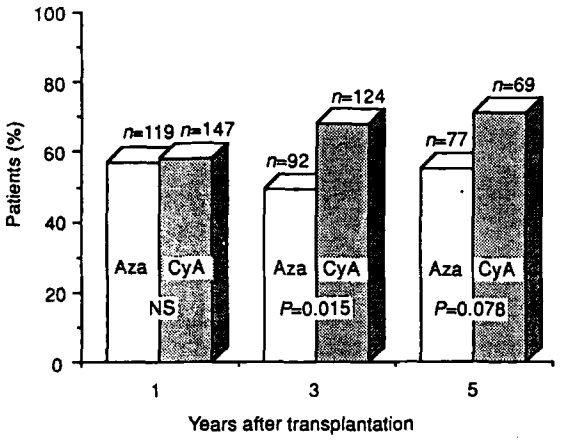

Fig. 4. Percentage of Aza/P-treated and CyA/P-treated *patients* on hypertensive drug treatment at 1, 3, and 5 *years after transplantation.* Significance between the groups are indicated (Chi-square test)

tion rate [4, 14, 21]. In addition, the variability of creatinine determinations between different laboratories has been reported to be as high as 15%–18% [10]. However, serial intrapatient measurements of serum creatinine and creatinine clearance performed in one single laboratory reflect the evolution of renal function in the individual patient rather well [14]. In our study, all determinations of creatinine in serum and urine were performed in the same laboratory, and the 24-h creatinine clearance was measured and not calculated by means of the Schwartz formula (derived from the reciprocal serum creatinine and parameters of body size) [22]. which was the case in several other studies [13, 19].

The first report on CyA-induced end-stage failure of previously healthy kidneys came from a study on adult heart transplant recipients [16]. Paraaminohippuric acid clearance and inulin clearance measurements and longitudinal histomorphometric examination of renal biopsies confirmed the chronic and progressive nature of the renal failure. Even after withdrawal of CyA, the renal injury was found to be irreversible.

In contrast, another group found the kidney function of CyA-treated heart recipients, as assessed by the mean slopes of reciprocal serum creatinine curves, to be impaired but stable [8].

In adult CyA-treated liver recipients, the function of their native kidneys, assessed by iothalamate clearance, was also impaired but stable after 2 years [5]. Native kidney function in CyA-treated pediatric liver recipients, however, was reported to decline serially within 3 years and to be progressive in the majority of cases [13]. Creatinine clearance was not measured but rather derived from serum creatinine measurements.

In adult kidney recipients, four different studies claimed impaired but stable function of the transplanted organ 2–5 years post-transplantation [2, 6, 7, 19]. However, these studies may be criticized for not including creatinine clearance, for short follow-up time [6, 19], and for including patients on simultaneous immunosuppression with CyA and azathioprine [7, 9], a combination thought to improve renal graft function [20].

Finally, in two small series, kidneys from pediatric donors were believed to be more sensitive to CyA than adult control kidneys [23], and pediatric recipients of kidneys studied up to 5 years post-transplantation had a continuous decrease in graft function and increasing incidence of hypertension [18].

Thus, in accordance with other studies in adult renal transplant recipients [2, 6, 7, 19], we found essentially stable renal function, as assessed by both serum creatinine and creatinine clearance, in patients treated with CyA as well as in patients treated with azathioprine. The CyA/P-treated patients had a glomerular filtration rate inferior to, or approximately two-thirds of, that in the Aza/P-treated patients. Unexpectedly, the Aza/P-treated patients, who subsequently lost their grafts, tended to have a faster decrease in creatinine clearance than the CyA/P-treated patients. This finding is perhaps explained by the clinically observed rapid progression of rejection in Aza/P-treated patients.

Hypertension is a well-known adverse effect of CyA treatment and is a risk factor for renal dysfunction. In the heart transplant recipients discussed earlier, Myers et al. found the incidence of arterial hypertension to be higher in the CyA-treated patients than in the Aza/P-treated controls (64% vs 6%) [16, 17]. In our renal transplant recipients there was no difference in incidence of hypertension at 1 year post-transplantation. However, we found a tendency towards an increased proportion of patients with hypertension with time in CyA/P-treated patients. This phenomenon may be dose concentration-related and remains to be evaluated.

We conclude that renal graft function, as estimated by serial serum creatinine and creatinine clearance determinations in patients under maintenance immunosuppression with CyA and corticosteroids, does not progressively deteriorate after 1 year post-transplantation. Aza/P-treated patients also had a stable graft function, although this was significantly better than that of CyA/P-treated patients. Thus, these data do not indicate a need to replace CyA with Aza in order to prevent chronic nephrotoxicity after renal transplantation.

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