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A randomized multicenter trial of cyclosporin and prednisolone versus cyclosporin, azathioprine, and prednisolone following primary living donor renal transplantation

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Abstract A total of 195 consecutive recipients of primary living donor renal transplants were randomized to receive either cyclosporin (CyA) and prednisolone (double therapy) or CyA, prednisolone, and azathioprine (triple therapy). There was no significant difference in patient or graft survival, incidence of acute rejection episodes, or major complications between the groups. The graft survival at 5 years was 71.5% in patients receiving double therapy and 71.6% in patients receiving triple therapy. In a Cox regression analysis, recipient age and occurrence of acute rejection were the only independently significant variables affecting graft survival, whereas treatment schedule did not. Renal function was stable throughout the observation period and did not differ between the double and triple therapy groups. A linear regression analysis showed that recipient age, donor age, gender, and occurrence of acute rejection significantly influenced the serum creatinine level. This and previous similar prospective studies in cadaveric renal transplantation indicate that there is no advantage of routinely adding azathioprine to a double drug regimen.

Key words Renal transplantation, immunosuppression
Immunosuppression, triple therapy, living donor · Living donor, immunosuppression, kidney

Introduction

Cyclosporin (CyA) has been a first choice immunosuppressive drug in organ transplantation for a decade now [4, 17]. Progress in clinical immunosuppression has mainly been achieved by empirical learning rather than from rigorous clinical trials. An example of this were the high doses of CyA used during the first years following its introduction, leading to the well-known nephrotoxic side effects [8, 27]. Another example is the introduction of the triple drug concept, i.e., a drug combination of CyA, azathioprine and prednisolone (or prednisone). Uncontrolled trials suggested that this combination would be superior to the previous standard therapy of CyA and prednisolone in controlling graft rejection and/or CyA-induced nephrotoxicity [13, 16, 38, 39]. Triple drug therapy rapidly spread and became the most common treatment choice within 3 years of its introduction [12]. However, other new treatment modalities, such as special treatment of immunized patients [31], the introduction of monoclonal antibody treatment [6], and antibacterial/antiviral prophylaxis [11, 15, 32, 36], all had an impact on graft outcome and rendered the interpretation of the effectiveness of triple therapy more difficult. Later randomized trials appeared. To date, none of these randomized trials suggests the superiority of triple over double drug therapy [3, 20, 24, 34].

In Sweden and Norway, a multicenter comparison of triple versus double drug therapy began in 1985. The objective of the study was to observe if renal transplant survival and/or function would be improved with triple therapy by lowering the CyA dose. Therefore, the CyA doses and the desired trough concentrations were higher in the double therapy than in the triple therapy group. There are

Table 1 Demographic data and distribution in double ($n = 100$) and triple ($n = 95$) therapy groups

Variable		n	Double therapy[a]	Triple therapy[a]	Probability level
Transplant center	1	26	13.0	13.7	NS
	2	19	10.0	9.5	NS
	3	41	22.0	20.0	NS
	4	109	55.0	56.8	NS
Renal disease	Chronic glomerulonephritis	94	44.0	52.6	NS
	Chronic pyelonephritis	13	7.0	6.3	NS
	Polycystic kidney disease	11	7.0	4.2	NS
	Hypertension	6	3.0	3.2	NS
	Diabetes mellitus	39	22.0	17.9	NS
	Other diseases	31	17.0	15.8	NS
Other pretransplant disease	Hypertension	91	51.1	55.7	NS
	Myocardial infarction	5	4.3	1.3	NS
	Peripheral vascular disease	5	3.3	2.5	NS
	Malignancy	3	1.1	2.5	NS
	Other	31	18.5	17.7	NS
Gender	Female	58	32.0	27.4	NS
Recipient age	Years	195	38.9 ± 15.4	41.2 ± 15.0	NS
Donor age	Years	190	51.5 ± 13.3	50.6 ± 12.5	NS
No. of mismatches in HLA-A + B + DR	0	13	8.0	5.3	NS
	1	27	14.0	13.7	NS
	2	79	44.0	36.8	NS
	3	59	26.0	34.7	NS
	4	8	4.0	4.2	NS
	5	8	3.0	5.3	NS
	6	1	1.0	0.0	
MLC, relative response	> 50 %	65	35.6	45.9	NS
Pretransplant dialysis	Never performed	72	38.0	35.8	NS
Pretransplant blood transfusions	None	103	52.0	53.7	NS

[a] Percent or mean ± SD

two parallel studies, one in cadaveric renal transplants [24] and one in living related renal transplants; the latter is reported in the present communication. In all, 195 living donor transplant recipients were studied during a 2-year period with a follow-up of 5 years. The present communication will present the survival, rejection incidence, complications, and renal function in the groups. In addition, the impact of demographic variables on long-term renal graft outcome will be discussed.

Patients and methods

Patients

A total of 195 primary living donor renal allograft recipients entered the present randomized trial (Second Scandinavian Multicentre Trial on CyA) between March 1985 and February 1987. The participating centres were Huddinge Hospital, Stockholm; National Hospital, Oslo; Sahlgrenska Hospital, Gothenburg; and Malmö General Hospital, Malmö. Exclusion criteria were cadaveric transplant, kidney from HLA-identical sibling, second or subsequent transplant, known intolerance by CyA or azathioprine, age below 16 years, and immunization requiring special immunosuppressive treatment. Informed consent was obtained prior to transplantation, whereafter the patients were randomly assigned to one of two treatment groups with either CyA and prednisolone (double therapy) or a lower dose of CyA, azathioprine, and prednisolone (triple therapy). The randomization was stratified center-wise so that the two groups were about equally large at all participating centers. The study was approved by the ethics committees of the participating hospitals and of the Swedish and Norwegian medical boards. The demographic data of the patients are displayed in Table 1. Follow-up was for a minimum of 4 years, and 74 % were followed for more than 5 years. No patient was lost to follow-up.

Techniques for tissue typing, crossmatching, and screening of antibodies in recipient pretransplant sera have been described in detail elsewhere [26]. Donors were primarily selected for HLA haploidentity by family testing. However, any degree of HLA haplotype mismatch between donor and recipient was accepted. One center also accepted family donors mismatched for two HLA haplotypes (17 spouses and 7 siblings). Any mixed lymphocyte culture (MLC) reactivity of recipient cells against donor-stimulating cells was accepted (ranging from 0 % to 254 % relative response). PRA positivity was defined as the presence of antibodies in a current serum (< 3 months prior to transplantation) reacting against separated T cells or nonseparated peripheral lymphocytes using the National Institute of Health (NIH) technique at 22 °C or the Kissmeyer-Nielsen technique at 37 °C. Two patients in the double therapy group and three patients in the triple therapy group were PRA-positive.

Table 2 Doses of CyA in the two treatment groups (mean ± SD)

Time after transplantation	Double therapy		Triple therapy		Probability level[a]
	n	mg/kg per day	*n*	mg/kg per day	
1 week	100	12.45 ± 3.59	93	9.59 ± 3.83	< 0.001
3 weeks	98	9.99 ± 3.95	89	8.08 ± 3.46	< 0.001
3 months	95	6.13 ± 2.29	86	5.03 ± 2.05	< 0.001
6 months	89	5.12 ± 1.91	82	4.37 ± 1.80	< 0.001
1 year	87	4.65 ± 1.51	82	4.14 ± 1.77	< 0.02
2 years	85	3.94 ± 1.25	74	3.60 ± 1.34	0.06
3 years	79	3.74 ± 1.30	73	3.60 ± 1.16	NS
4 years	74	3.40 ± 1.12	65	3.36 ± 1.00	NS
5 years	51	3.50 ± 1.07	47	3.24 ± 0.93	NS

[a] Mann-Whitney U-test

Donor-specific transfusions were not given and pretransplant blood transfusions were only given when medically indicated. All T-cell crossmatches were negative in a current serum and three patients in either group had a weakly positive B-cell crossmatch.

Double therapy

The 100 patients randomized to this treatment received CyA, 15 mg/kg per day, divided into two daily doses for 2 days prior to transplantation. On the day of transplantation, CyA was given intravenously in a dose of 7.5 mg/kg per day divided into three doses. Starting on day 1, CyA was given orally twice daily, beginning with 12 mg/kg and decreasing to 10 mg/kg per day on day 6. Thereafter, the CyA dose was adjusted, based on frequent trough whole blood concentrations of CyA determined by polyclonal radioimmunoassay (RIA) [9] to achieve whole blood concentrations of 400–800 ng/ml during the 1st month, 300–700 ng/ml during months 2 and 3, and 200–600 ng/ml thereafter. Table 2 shows the actual doses of CyA administered.

Triple therapy

The 95 patients randomized to this group received CyA, 15 mg/kg per day, for 2 days before transplantation, but no CyA was given on day 0. From day 1 onwards, CyA was given orally twice daily in a dose of 8 mg/kg per day. Thereafter, the dose was adjusted to achieve whole blood polyclonal RIA concentrations of 200–400 ng/ml during the 1st month, 150–350 ng/ml during the 2nd and 3rd months, and 100–300 ng/ml from the 4th month onwards. Furthermore, patients assigned to this group received azathioprine orally in an initial dose of 2 mg/kg per day, starting on the day of transplantation; this was reduced to 1 mg/kg per day on day 5.

All patients in both groups received steroids after transplantation. Prednisolone therapy, 30 mg/day, was started 2 days prior to transplantation. A single dose of 500 mg methylprednisolone was given intraoperatively. The prednisolone dose was increased to 100 mg/day on the day of transplantation and tapered by 10 mg/day until day 9, when a dose of 20 mg/day was reached. The dose was further reduced to 15 mg/day on day 22, and to a maintenance dose of 10 mg/day at 2 months after transplantation.

CyA was permanently discontinued in three patients on triple therapy; these patients were then given azathioprine and prednisolone. Azathioprine was permanently discontinued in tow patients on triple therapy. Furthermore, azathioprine was permanently instituted in 29 patients on double therapy, 16 during the 1st year, 9 during years 2 and 3, and 4 later after transplantation. The study was based on the intention to treat, and in the results all patients are assigned to their initial group.

Acute rejection episodes were clinically diagnosed based on physical examination and laboratory and sonographic data, preferably in combination with positive findings on a core needle biopsy and/or a fine needle aspiration biopsy. The diagnosis of acute rejection was confirmed by biopsy in 59% of the cases (54% in first, 68% in second, and 71% in third acute rejections). Primary treatment of acute rejection was with 500 mg of methylprednisolone on the 1st day and 250 mg on the following 3 days. When the rejection did not respond to the first treatment, either methylprednisolone was continued or a rabbit antithymocyte globulin preparation was given.

Statistical analysis

The statistical analyses were performed using the Medlog statistical package (Information Analysis, Mountain View, Calif., USA). Values are given as mean ± standard deviation (SD). The chi-square method with Yates' correction was used for comparison of the number of patients in different groups. The Wilcoxon matched pairs signed rank test or the Mann-Whitney U-test was used for not normally distributed paired or unpaired data, respectively. The log rank test (Mantel-Cox) was used to test the equality of survival. Stepwise linear regression and Cox regression [7] were performed using the Medlog statistical package as well as SOLO (BMDP Statistical Software, Los Angeles, Calif., USA). Creatinine clearance was calculated according to Cockcroft and Gault [5].

Deaths and complications were included in the analyses if the patients had been on dialysis treatment for less than 3 months following graft loss. No patients were excluded from survival analysis after randomization (and transplantation) had taken place.

Results

Patient survival

There was no significant difference in patient survival with double or triple therapy, the actual 1-year rates being 92.0% and 95.8% and the 5-year survival rates being 85.5% and 86.3%, respectively (Fig. 1). Nor were there differences in the causes of death between the treatment groups. The causes of death included: myocardial infarction (double therapy $n = 6$, triple therapy $n = 4$), infection (double therapy $n = 5$, triple therapy $n = 2$), malignancy

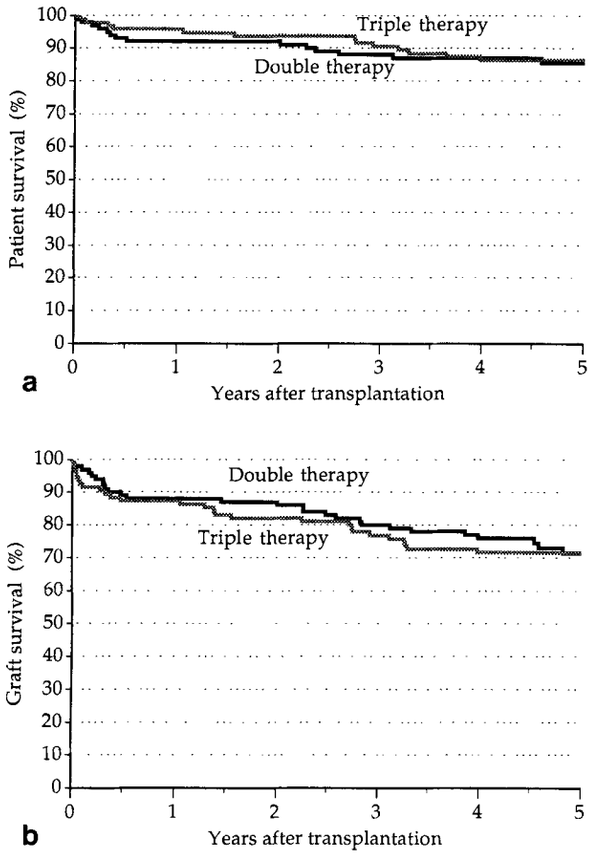

Fig. 1 **a** Patient and **b** graft survival in living donor renal transplant recipients randomized to double therapy ($n = 100$) or triple therapy ($n = 95$). P = NS

(double therapy $n = 1$, triple therapy $n = 4$), cerebral hemorrhage ($n = 1$ in each group), liver failure (double therapy $n = 1$) and unknown (triple therapy $n = 2$).

Graft survival

All grafts had immediate onset of function except for two in the triple therapy group with delayed onset. There was no significant difference in graft survival between the treatment groups. Actual 1-year survival rates were 88.0% and 87.4% in the double and triple therapy groups, respectively (Fig. 1). The corresponding 5-year survival rates were 71.5% and 71.6%, respectively. The estimated half-lives for grafts surviving more than 1 year were 15.0 years and 14.5 years in the double and triple therapy groups, respectively. Causes of graft loss were rejection (double therapy $n = 14$, triple therapy $n = 13$), death with a functioning graft ($n = 9$ in each group), and other (double therapy $n = 3$, triple therapy $n = 2$). Thus, rejection was the most common cause of graft loss during (54%) and after (50%) the 1st post-transplant year.

Twenty-four patients received grafts from spouses or siblings that were mismatched for two HLA haplotypes. The patient and graft survival rates in these patients did not differ significantly from those observed in patients with haploidentical grafts. The patient survival in the unrelated donors was 87.5% at 1 year and 75.0% at 5 years after transplantation; the graft survival was 79.2% at 1 year and 66.7% at 5 years.

Immunosuppressive drugs

The CyA dose differed significantly between the treatment groups during the 1st year after transplantation (Table 2). However, the target trough concentration ranges overlapped and at 1 year the doses only tended to differ; later on, the actual doses given were similar in the two groups. In violation of the study protocol, 16 patients on double therapy had their immunosuppressive therapy changed when azathioprine was added during the 1st year after transplantation; 13 other patients had a change of therapy more than 1 year after transplantation. These patients had a graft survival rate of 86.2% at 1 year and 75.9% at 5 years (no difference from those remaining on double therapy). No grafts were lost amongst patients having CyA medication discontinued ($n = 3$) or amongst patients having azathioprine discontinued ($n = 2$).

Acute rejection episodes

Of the 195 patients, 134 were treated for acute rejection, 69.0% in the double therapy group and 68.4% in the triple therapy group (P = NS). Seventy-five patients had one rejection (37.0% in the double and 40.0% in the triple therapy group; P = NS), 43 patients had two rejections (25.0% and 18.9%, respectively; P = NS), 12 patients had three rejections (6.0% and 6.3%, respectively; P = NS) and 4 patients had more than 3 acute rejection episodes.

The graft survival was excellent in the 61 patients who did not experience acute rejection: 93.4% at 1 year and 88.5% at 5 years. In contrast, the graft survival in patients who did experience acute rejection was 85.1% at 1 year and 66.5% at 5 years ($P < 0.0001$, log rank). The estimated graft half-lives were 46 years in patients not experiencing acute rejection and 12.7 years in patients with acute rejections. Patient survival did not differ significantly between rejecting and nonrejecting patients.

Complications

Table 3 lists the complications occurring in the two treatment groups. Except for more leukopenic episodes in the triple therapy group ($P < 0.01$) and more reports of tremor in the double therapy group, there were no differen-

Table 3 Infections, surgical complications, medical complications, and adverse events in the two treatment groups. The figures refer to the number of episodes in each group

Variable	Double therapy *n*	Triple therapy *n*	Probability level
Infectious episodes:			
Wound infection	8	7	NS
Urinary tract infection	42	32	NS
Bacterial pneumonia	17	15	NS
Bacterial septicemia	7	8	NS
Cytomegaloviral infection	9	14	NS
Surgical complications:			
Postoperative bleeding	4	2	NS
Urological complication	12	6	NS
Anastomosis of renal vessels	3	7	NS
Other surgical complication	9	4	NS
No. of post-transplant operations	20	15	NS
Medical complications:			
Worsened hypertension	45	34	NS
De novo hypertension	23	19	NS
Myocardial infarction	6	5	NS
Other heart disease	9	8	NS
Gastrointestinal bleeding	7	1	NS
Gastrointestinal perforation	0	1	NS
Diabetes mellitus	9	4	NS
CNS complications	4	2	NS
Venous thrombosis	3	1	NS
Arterial thrombosis	2	0	NS
Pulmonary embolism	0	3	NS
Other complications	33	37	NS
Adverse events:			
Hypertrichosis	64	31	NS
Tremor	28	11	< 0.01
Gingival hyperplasia	0	4	NS
Paresthesias	2	2	NS
Convulsions	4	0	NS
Liver dysfunction	29	21	NS
Renal dysfunction	128	115	NS
Leukopenia	1	12	< 0.01
Thrombocytopenia	1	2	NS
Malignancy	1	7	NS
Other adverse events	5	6	NS

ces in infections or in surgical or medical complications between the groups. Of all the patients, 91 had hypertension prior to transplantation and an additional 42 patients became hypertensive after transplantation resulting in a total of 68 % of all patients. The median number of days in the hospital following grafting were 24 in the double therapy group and 22.5 in the triple therapy group (P = NS).

Outcome in relation to demographic variables

In a univariate log rank analysis, the few patients with hypertension as the primary diagnosis did significantly worse than patients with any other disease (Table 4). Elderly recipients had a poorer graft survival due to a higher mortality rate. Grafts from elderly donors tended to be associated with a poorer outcome. HLA-A + B + DR mismatching had an influence on outcome. Graft survival was poor at one of the smaller centers. Factors that did not influence graft survival were gender, pretransplant dialysis, MLC reactivity, and pretransplant blood transfusions.

In a univariate Cox regression analysis, recipient factors significantly influencing graft survival were recipient and donor age, HLA mismatching, and occurrence of acute rejection (Table 5). In the stepwise multivariate Cox analysis, only recipient age and occurrence of acute rejection remained significant.

Renal function

Renal function, as assessed by serial determinations of serum creatinine and calculated creatinine clearance rates, did not differ between the treatment groups at any time

Table 4 Univariate log rank test of pretransplant variables with possible influence on graft survival. Factors without influence were gender, MLC, pretransplant dialysis, and pretransplant blood transfusions

Variable		*n*	Graft survival		Probability level[a]
			1 year	5 years	
Transplant center	1	26	96.2	46.9	< 0.05 vs 4
	2	19	89.5	73.7	
	3	41	82.9	78.0	
	4	109	87.2	76.1	
Renal disease	Chronic glomerulonephritis	94	85.1	72.7	
	Chronic pyelonephritis	13	92.3	76.9	
	Polycystic kidney disease	11	100.0	90.9	
	Hypertension	6	50.0	16.7	< 0.001 vs all others
	Diabetes mellitus	39	89.7	63.3	
	Other disease	32	93.7	81.2	
Recipient age	≤ 50	142	90.1	75.2	< 0.05
	> 50	53	81.1	62.3	
Donor age	≤ 40	39	87.2	87.2	< 0.05
	> 40	151	88.1	68.0	
No. of mismatches in HLA-A + B + DR	0	13	92.3	61.5	
	1	27	88.9	81.5	
	2	79	89.9	81.7	
	3	59	89.8	60.6	< 0.05 vs 2
	4	8	62.5	62.5	
	5	8	75.0	50.0	< 0.05 vs 2

[a] Log rank test

Table 5 Cox regression analysis of factors of possible importance for graft survival in living donor transplant recipients

Variable	Univariate analysis	Multivariate analysis		Probability level[a]
	P value	Odds ratio	Confidence interval	
Occurrence of acute rejection	0.0051	3.550	1.571–8.020	0.0023
Recipient age	0.0089	1.021	1.001–1.042	0.038
No. of HLA-A + B + DR mismatches	0.013			0.30
Donor age	0.038			0.29
Pretransplant dialysis	0.12			
Transplant center	0.13			
Polycystic kidney disease	0.19			
Haploidentical vs nonrelated donor	0.25			
Pretransplant blood transfusions	0.26			
Diabetes mellitus	0.26			
Gender	0.50			
Relative response in MLC	0.55			
Disease of pyelonephritis	0.64			
Double vs triple therapy	0.75			
Disease of glomerulonephritis	0.86			

[a] Chi-square statistics (4 df) = 21.88, $P < 0.0005$

after transplantation. Furthermore, renal function was stable from 1 to 5 years after transplantation. Figure 2 depicts the median calculated creatinine clearance rates in the two groups. In a stepwise linear regression analysis using the same variables as in the Cox model above, the 1-year creatinine clearance was significantly and independently influenced by recipient age ($P < 0.0001$), donor age ($P < 0.0001$), gender ($P < 0.001$), and whether or not an acute rejection occurred during the first 6 months ($P < 0.002$). Thus, the creatinine clearance at 1 year after transplantation was 58.6 ml/min in grafts from donors below 55 years of age and 46.0 ml/min in grafts from donors 55 years old or older ($P < 0.001, r = -0.42$). Furthermore, the 1-year creatinine clearance was 56.1 ml/min in recipients aged below 55 years and 43.6 ml/min in recipients aged 55 years or older. There was only a slight tendency for donor-recipient age matching ($r = 0.20$). Furthermore, patients who had acute rejection episodes during the first 6 months had a 1-year creatinine clearance of 52.1 ml/min versus 57.4 ml/min in patients without rejection ($P < 0.05$).

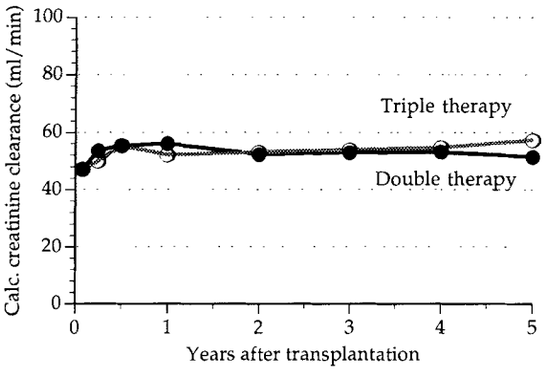

Fig. 2 Calculated creatinine clearance rates 1–5 years after transplantation. P = NS

Discussion

Immunosuppression for renal transplantation has been based on CyA and prednisolone for a decade [17]. In spite of the superiority of this treatment over previous immunosuppressive therapies, graft rejection remains a major cause of graft loss [14]. In an attempt to improve immunosuppression, CyA, prednisolone, and azathioprine were combined [13, 16, 38, 39]. It was hoped that this would allow for a reduction in the CyA dose (and cost) and/or potentiate the immunosuppressive effect of CyA. However, recent in vitro data suggest that azathioprine only exerts an additive effect with CyA [18]. Furthermore, none of the randomized trials of triple drug therapy have been able to present a significant difference in graft survival between double and triple therapy [3, 20, 34].

To finally elucidate the principle of triple drug therapy, we performed two trials: one in cadaveric donor [24] and one in living donor renal transplantation. These two trials present the largest randomized trials on this subject, and the present investigation is the only such study performed in living donor transplantation. The findings are straightforward, indicating that azathioprine in the dose given did not improve the results following living donor renal transplantation. There were no differences between the two treatment groups regarding graft and patient survival, rejection incidences, infections, or other complications.

However, two points of criticism may be raised. Firstly, due to nephrotoxicity or recurrent rejection 16% of the double therapy patients had their immunosuppressive therapy changed with the addition of azathioprine during the 1st year after transplantation and 13% had azathioprine added after the 1st post-transplant year. It is difficult to assess the impact of this change in therapy, which was performed in violation of the study protocol. If azathioprine had a favorable effect in this situation, there might have been difference in survival. However, there was no difference in graft survival between patients who received additional azathioprine medication and those who remained on double drug therapy. Secondly, the total number of patients in this living donor study was small. A power calculation [10] revealed that based on a power of 80%, a crude median survival time of 10 years, and a follow-up of 5 years, the total number of patients required to find a 50% increased risk of graft loss in either group was 384. The main reason for the large number of patients required was the excellent median survival. A similar analysis in cadaveric renal transplant recipients with a crude median survival time of 5.5 years showed that 252 patients were required. The number of patients entered in the previous randomized trials were 86 [34], 80 [20], 209 [3], and 463 [24], suggesting that the first two studies were smaller than statistically required.

Why, then, does azathioprine not affect renal allograft survival? Even if the drug is only additive to CyA, this does not explain the total absence of effect on graft survival. One possible explanation is inadequate dosing of azathioprine, resulting in a dose that is too low for a majority of the patients. It has recently been demonstrated that azathioprine displays intra- and interindividual pharmacokinetic variabilities that are almost twice as large as those of CyA [23, 28–30]. Thus, after oral dosing, a more than threefold intraindividual and a more than 15-fold interindividual variability in the pharmacokinetics of azathioprine was observed [28]. Considering that azathioprine is usually administered according to body weight and that no pharmacological monitoring is performed, one can only conclude that drug concentrations must be inadequate in a majority of the patients. Two important recent advances make azathioprine monitoring possible. Firstly, it is now possible to measure azathioprine in blood after oral dosing [28]. Secondly, samples collected 2 h after dosage relate closely to the area under the concentration time curve (AUC). Thus, this sampling time may serve as a monitoring tool since azathioprine has a short half-life and is undetectable after 6–10 h.

At the time the present study was designed, it was feared that the combination of CyA with high-dose azathioprine would potentiate immunosuppression to the extent that infections would be more frequent. However, since studies such as ours have proved that this is not the case, recent triple drug regimens often include higher azathioprine doses.

In the present study, patient survival was excellent, with most patients alive 5 years after transplantation. In agreement with mortality figures from northern European transplant registries, the most common cause of death was myocardial infarction [12]. Ischemic heart disease will become even more common as the transplant population grows older. Graft survival was also fairly good, with an estimated graft half-life of 14.5–15 years. The major impact of acute rejection on graft loss was reflected in the difference in graft half-life between patients who did and those who did not suffer from acute rejection (12.7 versus 46 years, respectively).

The graft survival in two HLA-haplomismatched transplants was slightly poorer than that in haploidentical transplants. Although there was no significant difference between these groups in the present study, it is hypothesized that, in general, the survival of unrelated transplants is somewhere in-between that of living related and cadaveric renal transplants [2, 33, 37, 41].

The well-known poor prognosis in nephrosclerosis/hypertension and diabetes mellitus was confirmed in the present study [21, 22]. Furthermore, living related transplantations performed in patients with polycystic kidney disease were associated with an excellent graft survival.

The two variables that influenced graft survival in the multivariate analysis were recipient age and occurrence of acute rejection, whereas donor age and HLA mismatching had an influence only in the univariate analysis. This is in agreement with a previous study in which we found no effect of HLA matching on graft survival in haploidentical living related transplants [1]. Others have found an influence of donor age on graft survival [35, 40], and it is possible that this would have had a significant impact if the number of patients had been larger. Interestingly, MLC reactivity had no influence on graft survival.

Any aging kidney suffers from irreversible loss of function. In agreement with previous studies, this was reflected in the poorer renal function in recipients of kidneys from elderly donors [19]. However, this does not explain why recipient age would influence graft function. Thus, there must be additional explanations for this highly significant finding. One such factor may be a reduced cardiac output leading to a reduction in renal blood flow. That acute rejection may damage the kidney was reflected in a poorer graft function in kidneys suffering from acute rejection. This is also in agreement with previous reports [25, 42]. However, in contrast to our previous experience, MLC reactivity did not influence rejection incidence [1].

In conclusion, the present study in primary living donor transplantation, together with several trials in primary cadaveric renal transplantation, found no difference in graft survival between double and triple therapy. Thus, treatment with CyA and prednisone/prednisolone seems sufficient as initial treatment in all primary renal transplants.

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