Original articles

TRANSPLANT International

Transplant Int (1990) 3: 121–127

Renal allograft immunosuppression

II. A randomized trial of withdrawal of one drug in triple drug immunosuppression

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Received January 2, 1990/Received after revision March 28, 1990/Accepted April 2, 1990

Abstract. A prospective randomized study was conducted to evaluate the impact of four different conversion protocols on graft outcome in long-term follow-up. Between January 1986 and May 1987, 128 patients with first cadaveric kidney allografts were randomized at the time of transplantation to four treatment groups of 32 patients each, to be assigned 10 weeks post-transplantation. During the first 10 weeks, all patients received triple therapy with low-dose azathioprine (Aza), cyclosporin (CyA), and methylprednisolone (MP). After 10 weeks, one group continued with triple therapy (group A) while the three other groups received different combinations of two drugs, namely, Aza and CyA (group B), Aza and MP (group C), or CyA and MP (group D). Withdrawal of MP (group B) or especially of CyA (group C) was associated with 4/29 (14%) and 10/28 (36%) acute rejection episodes, respectively, for 60 days after conversion. All rejections were mild and reversible. There were no rejections after Aza withdrawal or in the group that continued on triple therapy during the corresponding time period. The most common reason for dropping out after withdrawal, for those patients who could not continue on the originally randomized medication, was azathioprine intolerance ($n = 12$). Five patients were switched back to triple therapy after CyA withdrawal due to rejection. Steroid intolerance was rare and CyA in low doses was very well tolerated. At 1 year there were no statistically significant differences in graft survival between groups A, B, C, and D – 81%, 88%, 88%, and 88%, respectively – or in patient survival – 88%, 88%, 88%, and 97%, respectively. For those patients continuing with the originally randomized treatment protocol, there were no differences in patient or graft survival either, the means being 91% and 89%, respectively. The most common cause of death after withdrawal was cardiovascular in nature, and there were no more fatal infections under triple drug treatment than with double drug regimens. There were no statistically significant differences in mean serum creatinine values at 1 year. The median serum creatinine values for groups A, B, C, and D were 112, 132, 133, and 133 μmol/l, respectively. At 1 year the mean CyA dose in the groups that continued with CyA was 3.5–4.2 mg/kg per day and CyA concentrations were equal.

Key words: Triple therapy, in kidney transplantation – Conversion, in kidney transplantation

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The three main immunosuppressive drugs – cyclosporin A (CyA), azathioprine (Aza), and methylprednisolone (MP) – affect at different sites of the immune response [6, 12, 13, 16]. Use of all three drugs together would thus enable maximization of the immunosuppressive effect, redistribution of unwanted side effects, and, possibly, reduction of the doses of each individual drug. On the other hand, triple drug treatment may be dangerous in the long run, as the long-term side effects of very intensive immunosuppression are not known.

The purpose of this trial was to compare various immunosuppressive protocols in a single center study, with a special emphasis on long-term effects and side effects. This trial was designed to investigate whether it is safe to withdraw one of the three drugs once the period of highest risk of rejection is over and whether it is safe to continue with long-term triple drug treatment.

All 128 patients in this prospective study were on triple drug treatment (CyA, Aza, and MP) during the first 10 weeks post-transplantation. After these 10 weeks, the patients were assigned to one of four final treatment groups, according to a pre-established randomization protocol. One group continued with triple therapy (group A), while the three other groups received different combinations of two drugs, namely Aza and CyA (group B), Aza and MP (group C), or CyA and MP (group D). This report describes the results of conversion up to 1 year.

Table 1. Characteristics of patients and transplants on entry. Values represent mean ± SD. Aza, Azathioprine; CyA, cyclosporin; MP, methylprednisolone. All differences are nonsignificant ($P > 0.05$)

Initial immunosuppression Conversion at 10 weeks to	Group A Aza + CyA + MP Aza + CyA + MP	Group B Aza + CyA + MP Aza + CyA	Group C Aza + CyA + MP Aza + MP	Group D Aza + CyA + MP CyA + MP
Number	32	32	32	32
Male/female	20/12	15/17	17/15	17/15
Age (years)	47 ± 11	49 ± 13	45 ± 12	43 ± 13
First grafts (%)	100	100	100	100
Primary renal disease (%)				
Glomerulonephritis	41	28	31	28
Diabetic nephropathy	19	16	16	34
Preoperative dialysis treatment (%)				
Hemodialysis	59	50	59	47
Peritoneal dialysis	41	50	41	53
Time in dialysis (months)	17 ± 19	12 ± 8	12 ± 8	12 ± 12
Weight/height ratio (kg/cm)	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1
Histocompatibility				
AB mismatches	1.5 ± 0.6	1.4 ± 0.8	1.4 ± 0.8	1.5 ± 0.7
DR mismatches	1.0 ± 0.6	0.9 ± 0.8	0.9 ± 0.5	0.9 ± 0.7
No preformed antibodies (%)	85	85	97	83
Average number of transfusions	9 ± 12	7 ± 6	6 ± 5	8 ± 11
Cold ischemia (hours)	31 ± 7	31 ± 7	29 ± 6	29 ± 7

Patients and methods

Patients

Beginning in January 1986, 128 consecutive eligible adult patients with first cadaveric kidney allografts were prospectively randomized, using the sealed envelope method, into four different immunosuppressive protocols to be assigned 10 weeks post-transplantation. The informed consent of the patient was given prior to the operation. A sealed, serially numbered envelope was opened after transplantation (admission before randomization). The last recipient included in the study was transplanted in May 1987. Each immunosuppressive group included 32 patients.

During this same time period, a total of 184 renal transplantations were performed in our center. Nineteen of these patients received living related transplants, 22 had second transplants, 4 received third grafts, and 2 were children. Nine patients with first cadaveric grafts were excluded from the study. Seven of the nine excluded patients had diabetes and were in poor general condition, and five of these had such infectious problems from the beginning of transplantation that triple drug treatment could not be used. One diabetic patient got paraplegia of unknown cause on the 1st day postoperatively and another one died of cardiac infarction shortly after transplantation. Two of the nine excluded patients had glomerulonephritis; one of these had hepatic cirrhosis of unknown cause and the other one, a man over 60 years of age, lost his graft because of arterial thrombosis and underwent transplantectomy with a graft that never functioned. Thus, exclusions from the study were for medical reasons, mainly on the grounds that triple therapy was not considered suitable for these patients.

Initial immunosuppression

During the first 10 weeks, all 128 patients included in the study received triple drug immunosuppression with CyA, Aza, and MP. A single oral dose of 5 mg/kg CyA was given preoperatively; Aza and MP were started at the beginning of the operation. CyA was administered at a dosage of 10 mg/kg per day initially starting on the 1st day and was later adjusted to whole blood trough levels (polyclonal RIA was used until the end of January 1988 and later on monoclonal CyA parent molecule-specific RIA). A CyA assay was carried out twice weekly during the 1st weeks. Aza was initiated at a dosage of 2 mg/kg per day and tapered to 1 mg/kg per day on the 14th day. The MP dose was 1 mg/kg per day initially, tapering gradually at 3-day intervals to 0.25 mg/kg per day on the 10th postoperative day.

Immunosuppression after conversion

At 10 weeks, triple therapy for all patients consisted of 1 mg/kg per day Aza, 12–16 mg daily MP, and CyA according to whole blood trough levels. After 10 weeks, according to randomization, one of the four groups continued with triple drug treatment (group A) while the three other groups continued with different double drug combinations: CyA and Aza (group B), Aza and MP (group C), and CyA and MP (group D). In group A, the MP dose was tapered to 4–12 mg daily during the 1st year. In group B, the dose of Aza was temporarily increased to 2 mg/kg per day and later adjusted to blood white cell count. The steroids were gradually withdrawn over a period of 1–2 weeks. In group C, CyA was discontinued abruptly, Aza was returned to 2 mg/kg per day, and MP was elevated temporarily to 0.5 mg/kg per day, tapering later as in group A. In group D, Aza was discontinued abruptly and MP was decreased later on as in the other groups. CyA was maintained at the preconversion level. From conversion at 3 months to 6 months postoperatively, the CyA dose was adjusted to maintain blood concentration of 200–600 ng/ml and subsequently, after 6 months, of 150–400 ng/ml using the polyclonal RIA method. Later on, when using the monoclonal parent molecule-specific RIA method, after 3 months, the maintenance level of CyA was 60–120 ng/ml.

Diagnosis and treatment of rejection

Diagnosis of rejection was based on clinical symptoms and signs and was verified by fine needle aspiration biopsy (FNAB). Episodes of acute rejection were treated with oral MP (3 mg/kg per day) for 5 days. In a few rejections, all of which were in the group where CyA had been discontinued, CyA was then added for immunosuppres-

Table 2. Graft losses and drop-outs before conversion and after conversion up to 1 year

Final randomization group	Number of randomized patients	Patients with originally planned medication before conversion (at 10 weeks)[e]	From 10 weeks to 1 year				
			Grafts lost			Dropouts	Patients remaining in trial at 1 year with originally planned medication
			Deaths	Dialysis	Total		
A: Aza + CyA + MP	32	32	4	2	6	4[a]	22
B: Aza + CyA	32	29	3	–	3	8[b]	18
C: Aza + MP	32	28	3	–	3	11[c]	14
D: CyA + MP	32	29	–	2[f]	2	4[d]	24
All groups	128	118	10	4	14	26	78

[a] 4 Aza intolerance
[b] 4 Aza intolerance, 4 back to triple treatment
[c] 4 Aza intolerance, 5 back to triple treatment, 2 steroid intolerance
[d] 1 back to triple treatment, 1 steroid intolerance, 1 CyA intolerance, 1 patient neglected treatment and control admissions
[e] Before conversion, all patients were on triple treatment. Prior to conversion three deaths were recorded, one each in groups B, C, and D The other one dropped out before conversion (CyA intolerance)
[f] Six drop-outs (five for Aza intolerance, one for CyA intolerance) were recorded: two in group B, three in group C, and one in group D One lost a graft (group D) because of a transplant that never functioned

sion as rejection treatment. No patients needed antithymocyte globulin after conversion for a steroid-resistant rejection.

Backgrounds of the patients

Backgrounds of the patients are presented in Table 1. HLA matching was used for patient selection. All patients had received at least three units of blood, and all were on dialysis prior to transplantation. A negative T-cell crossmatch was mandatory for transplantation.

Monitoring during conversion at 10 weeks

After 70 days post-transplantation, all patients were called to the hospital for conversion and were followed up as inpatients for 1–2 weeks during conversion. FNAB was taken before conversion and one to three times after conversion. FNAB was taken more often when CyA or MP was withdrawn.

Statistical analysis

Graft loss was defined as returning to maintenance dialysis or as patient death with a functioning graft. The graft and patient survival values are actual. For group comparisons, analyses of variance for parametric data and the chi-square test were used or Fischer's exact test when appropriate. Differences at the level of $P < 0.05$ were considered significant.

Results

Characteristics of patients

The four groups did not differ in age, sex ratio, dialysis type, or time in dialysis. HLA-A, B, and DR matching were equal, as were the number of transfusions preoperatively. Mean cold ischemia time was the same. The causes of renal failure in each group did not differ. Overall, 32% of the patients had glomerulonephritis, 21% diabetes, 14% polycystic kidneys, 13% pyelonephritis, 11% other types of nephritis, and 9% suffered from other causes. Thirty-four percent of the patients in group D (CyA and MP) had diabetes, but the difference was not statistically significant compared with the other groups (16%–19% diabetic patients). Group C (Aza and MP) contained more patients without preformed antibodies against the random panel of 24, but this was not a statistically significant difference ($P > 0.05$).

Patients remaining in trial at 10 weeks

Altogether, 118 of the 128 randomized patients tolerated triple drug treatment up to 10 weeks post-transplantation. Six patients dropped out, three patients died, and one patient had a graft that never functioned. At the time of conversion, all 32 patients in group A remained in the trial. In group B, 29 patients were on the originally planned medication; one patient had died and two patients had dropped out. Group C still included 28 of the 32 patients; one patient had died and three patients had dropped out. Group D still included 29 patients; one patient had died, one patient had a graft that never functioned, and one patient had dropped out. Thus, the final groups A, B, C, and D, where elective drug withdrawal was attempted, included 32, 29, 28, and 29 patients, respectively, all of whom were maintained up until 10 weeks on triple immunosuppression.

The causes of the three deaths were cardiac infarction, rupture of aortic aneurysm, and fulminate respiratory infection of unknown cause 40 days, 26 days, and 45 days postoperatively, respectively. All patients died with a functioning graft, and their mean serum creatinine value at the time of death was 124 ± 27 μmol/l.

The most common reason for preconversion drop-out was azathioprine intolerance, either because of leukopenia ($n = 2$), elevated transaminase levels ($n = 2$), or re-

Table 3. Causes of death after conversion from 10 weeks to 1 year

Cause	Group			
	Aza + CyA + MP	Aza + CyA	Aza + MP	CyA + MP
Cardiovascular	1	2	1	–
Infection	3[a]	–	–	–
Ketoacidosis	–	1	–	–
Gastrointestinal bleeding + cytomegalovirus infection	–	–	1	–
Suicide	–	–	1	–
Total	4	3	3	0

[a] Two patients were drop-outs on CyA and MP before death

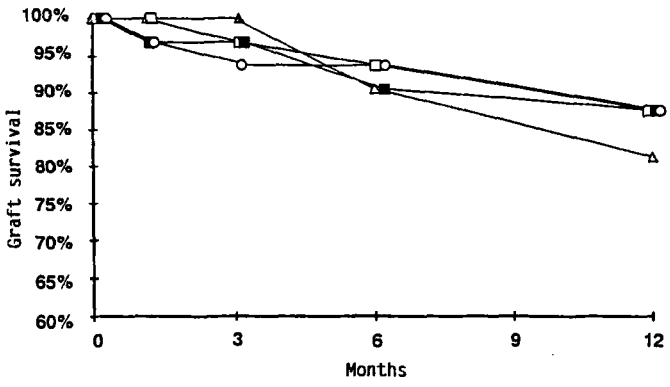

Fig. 1. One-year actual graft survival in triple therapy and different double therapy groups. △, Triple therapy; □, Aza + CyA; ■, Aza + MP; ○, CyA + MP. P = NS (chi-square test)

duced immunosuppression as a result of cessation of Aza during pulmonary infection (n = 1). In one case, CyA toxicity was suspected due to hemolytic syndrome and CyA was discontinued 28 days postoperatively. One patient had a graft that never functioned.

Reasons for dropping out and graft losses from 10 weeks to 1 year

All patients passed the 1-year follow-up. Drop-outs and graft losses after conversion from 10 weeks to 1 year are presented in the Table 2. The number of patients remaining in trial with the originally planned medication at 1 year was 22, 18, 14, and 24 in groups A, B, C, and D, respectively.

Azathioprine intolerance was the most common reason for dropping out (n = 12). Four patients in group A who should have continued on triple drug treatment dropped out because of Aza intolerance; one patient had elevated liver transaminases and three had leukopenia. Four patients in group B and another four in group C, all continuing with Aza, also dropped out because of leukopenia. In four of the twelve cases, leukopenia was associated with suspected viral infection. The patients had symptomatic disease with fever, and the early antigen of cytomegalovirus was positive in the urine in three cases. Unfortunately, blood was not tested for cytomegalovirus at that time. There were no differences in infections between the four groups. This will be reported in more detail in a subsequent communication.

The highest frequency of drop-outs – eleven patients – was in group C (Aza and MP). Five of these patients were switched back to triple drug treatment because of acute rejection during conversion. Switching back to triple drug treatment was the second most common reason for dropping out (n = 10). In group B (Aza and CyA), four patients were switched back to triple drug treatment, two because of acute rejection and two others because there was impairment of renal function with suspicion of chronic rejection. In group D, one patient was switched to triple drug treatment after impairment of graft function.

Methylprednisolone was discontinued for two patients in group C and for one patient in group D, in the former because one patient suffered spontaneous bone fractures and in two others because of very serious acne. Suspected activation of the lymphoroliferative system resulted in the cessation of CyA administration in one case in group D. Another patient in group D neglected treatment and thus became a drop-out.

If and when one of the drugs was discontinued because of its side effects in the double drug regimen groups, the third immunosuppressive agent, which was withdrawn during conversion, was permanently returned. Seven patients were switched back to triple therapy because of acute rejection. Three more patients were returned to triple therapy for other reasons. All drop-outs were followed up later, as were the other patients.

The causes of death after conversion at 10 months to 1 year are presented in Table 3. Total graft losses from the beginning of the study up to 1 year and changes in treatment at 1 year are presented in Table 4. From 10 weeks to 1 year, ten patients died, eight with a functioning graft (mean serum creatinine 236 ± 124 μmol/l). Two other patients, who succumbed to infection, lost their grafts 1–2

Table 4. Total graft losses after transplantation and changes in treatment at 1 year

		Final randomization group			
		A Aza + CyA + MP (n = 32)	B Aza + CyA (n = 32)	C Aza + MP (n = 32)	D CyA + MP (n = 32)
Graft losses					
Death		4	4	4	1
Dialysis[a]		2	0	0	2
Graft that never functioned		0	0	0	1
Total		6	4	4	4
Drop-outs Treatment changes to:					
CyA + MP	(Aza intolerance)	4	6	7	–
Aza + MP	(CyA intolerance)	–	–	–	1
Aza + CyA	(steroid intolerance)	–	–	2	1
Aza + CyA + MP	(returned to triple therapy)	–	4	5	1
Other		–	–	1[b]	–
Treatment after randomization		22	18	14	24

[a] Grafts lost to chronic rejection
[b] Unknown medication, patient noncompliance

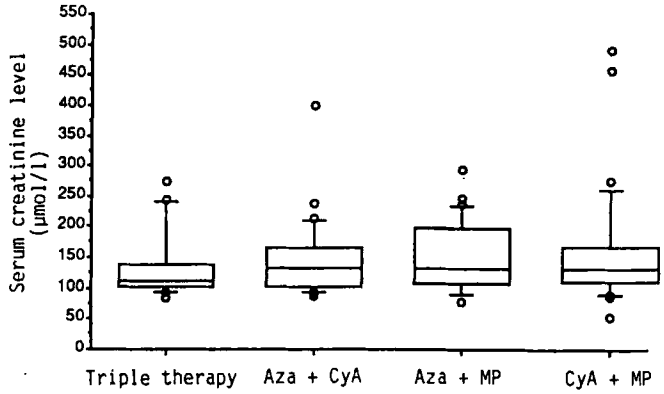

Fig. 2. Median serum creatinine values in triple therapy and different double therapy groups at 1 year. Plot showing 10th, 25th, 50th, 75th and 90th percentiles

weeks before they died. The most common cause of death after conversion was cardiovascular. In group A, which continued on triple treatment, three deaths resulting from infection were recorded, yet two of these patients had already been given a new treatment regimen (i.e., were drop-outs). The patient dying of gastrointestinal bleeding under immunosuppression with Aza and MP (group C) had a serious cytomegalovirus infection, which led to many complications, bleeding being the last one.

Looking only at the diabetic patients and their success on the originally planned medication, there was one who dropped out because of CyA toxicity (group D), two who were returned to dialysis (one in group A and one in group D), and five who died. Nineteen of 27 diabetic patients (70%) were on the originally planned medication at 1 year. The overall 1-year graft survival was 74% for the diabetics.

Graft and patient survival at 1 year

Graft and patient survival are presented in Tables 5 and 6 and in Fig. 1. For patients on the originally planned medication, the 1-year graft and patient survival rates were the lowest in group C (82%) compared to the total average graft and patient survival rates (86% and 90%, respectively; P = NS). The lowest graft survival for all patients in each group was recorded in group A (81%). In fact, there were no statistically significant differences between the four groups, either for patient or graft survival, even when considering only patients with the originally planned medication or all patients in each group.

For reference, graft and patient survival for all cadaveric allografts, including first, second, and subsequent grafts in the same center at the corresponding time period, were 82% and 88%, respectively.

Rejections after conversion

Clinical acute rejection episodes developed only in the groups where either steroids or CyA was withdrawn. There were no rejections after conversion in group A (continued triple drug treatment) during the corresponding time period or in group D (CyA and MP) after the abrupt discontinuation of Aza. In group B (Aza and CyA), 4 of 29 patients (14%) had a rejection episode within 60 days after conversion; all of these rejections were reversible. The mean time between rejection and conversion was 31 ± 21 days. The incidence of postconversion acute rejection in group C (Aza and MP) was the highest: 10 of 28 patients (36%) (Table 7). The incidence of rejection was significantly higher in group C than in the other groups ($P < 0.001$). At the beginning of the study, CyA was withdrawn abruptly from the first patients, but in later patients in this group by tapering the dose to zero within 1 or 2 weeks. In this group, acute rejection episodes occurred as early as 9 days and as late as 57 days postconversion, the mean time being 22 ± 14 days. In group C, eight rejections were treated with MP and two by adding CyA back to the treatment regimen. It is worth noting that no graft losses were recorded at this period in any one of the four groups.

Fine needle aspiration biopsy was taken from every patient before conversion and one to three times afterwards. The mean corrected increment (CI) before conversion in groups A, B, C, and D were 1.8 ± 1.5, 1.8 ± 1.2, 1.7 ± 1.4, and 1.6 ± 0.9, respectively, indicating only a very small inflammation in the graft. The peak CIs of the same groups for 2 weeks after conversion were 2.4 ± 1.8, 2.9 ± 2.0, 2.4 ± 1.7, and 1.8 ± 1.0. The mean CIs in groups B and C, just before conversion, were 2.9 and 2.3 for those who experienced rejection afterwards and 1.6 and 1.4 for those who did not. The difference was not significant ($P < 0.1$).

In both group A and group D, two patients lost their grafts to chronic rejection. Two of these patients had diabetes. Three of the four patients had CyA as part of their medication all of the time. Due to a lack of core biopsy evidence, the possibility of CyA toxicity cannot be ruled out.

Graft function and CyA concentrations at 1 year

At 10 weeks before conversion, graft function and CyA concentration were equal in all final groups. The mean serum creatinine for all patients was 143 ± 68 µmol/l,

Table 5. Graft survival

Group	At 10 weeks	At 1 year	
		Patients with originally planned medication	All patients in a group
Aza + CyA + MP	100%	88%	81%
Aza + CyA	97%	90%	88%
Aza + MP	97%	82%	88%
CyA + MP	94%	92%	88%
All groups	97%	89%	86%

Table 6. Patient survival

Group	At 10 weeks	At 1 year	
		Patients with originally planned medication	All patients in a group
Aza + CyA + MP	100%	92%	88%
Aza + CyA	97%	90%	88%
Aza + MP	97%	82%	88%
CyA + MP	97%	96%	97%
All groups	98%	91%	90%

Table 7. Rejections in different treatment groups before and after conversion

Before conversion[a]				After conversion			
Treatment	Number of rejections	Percentage of patients with rejection	Number of rejection episodes/patient	Final randomization group	Number of rejections within 90 days	Percentage of patients with rejection	Number of rejections up to 1 year
A: Aza + CyA + MP	11	34%	0.34	A: Aza + CyA + MP	0	0%	1
B: Aza + CyA + MP	7[b]	19%	0.22	B: Aza + CyA	4	14%	6
C: Aza + CyA + MP	6[c]	13%	0.19	C: Aza + MP	10	36%	12
D: Aza + CyA + MP	12[d]	31%	0.38	D: CyA + MP	0	0%	1
Total	36	24%	0.28				

[a] Before conversion, during the first 10 weeks, all patients were on triple drug treatment
[b] In six patients
[c] In four patients
[d] In ten patients

Table 8. Renal function of all patients and patients with originally planned medication at the end of 1st year. Values represent mean ± SD. F, all patients with functioning grafts; O, patients continuing with originally planned medication

Group	Patients with functioning grafts (F) *n*	Patients with originally planned medication (O) *n*	Creatinine (μmol/l) F	Creatinine (μmol/l) O	CyA concentration[a] (ng/ml) F	CyA concentration[a] (ng/ml) O	CyA dose (mg/kg) F	CyA dose (mg/kg) O
A: Aza + CyA + MP	26	22	133 ± 55	140 ± 58	276 ± 102	284 ± 103	4.2 ± 3.2	4.2 ± 2.7
B: Aza + CyA	28	18	145 ± 64	133 ± 40	312 ± 84	329 ± 88	3.5 ± 1.4	3.7 ± 1.2
C: Aza + MP	28	14	152 ± 59	149 ± 64	273 ± 113	–	4.6 ± 1.9	–
D: CyA + MP	28	24	164 ± 100	136 ± 49	289 ± 98	295 ± 98	4.0 ± 1.2	4.1 ± 1.2

[a] Trough whole blood level

serum urea 11.3 ± 6.3 mmol/l, creatinine clearance 58 ± 22 ml/min, CyA concentration 532 ± 208 ng/ml, and CyA dose 6.3 ± 2.4 mg/kg.

The mean creatinine values at 1 year are presented in Table 8. There were no differences in graft function between the four groups on the originally planned medication. Those who dropped out in each group usually had higher creatinine values than those with the originally planned medication (in groups B, C, and D), but a statistically significant difference was present only in group D (CyA + MP). The reason for this is that one of the four patients who dropped out in that group and who neglected check-ups did not cooperate; in this patient graft function rapidly decreased. In group A, the triple drug treatment group, the drop-outs had the lowest creatinine values and all of these patients had CyA in their medication. The median serum creatinine values, changing from 112 to 133 μmol/l with 10th and 90th percentiles, are presented in Fig. 2.

CyA doses were equal in each group at 1 year (Table 8). In group C, all 14 patients on CyA were drop-outs, and the mean CyA dose (4.6 mg/kg) was a little higher but not statistically significant. CyA concentrations are presented only for those patients who were assayed by the whole blood polyclonal RIA method. There were in each group, however, some patients who passed the 1-year checkpoint after the method was changed to monoclonal.

Discussion

At 1 year there were no differences between the groups: graft and patient survival for patients continuing with the originally planned medication and for all patients in a group were equal, without any statistically significant differences. Considering the whole time period from transplantation to the end of the 1st year, it is worth noting that graft and patient survival, on most occasions, was nearly the same, confirming the fact that irreversible acute rejection was no longer a problem. Nearly all graft losses were due to loss of the patient with a functioning graft. In our study, the mean rejection frequency per patient before conversion was 0.28. In fact, no grafts were lost to acute rejection in this study. Nor were any graft losses due to rejection recorded in any one of the four groups at the time of conversion.

Many studies have reported higher creatinine values for patients using CyA from the beginning [1, 2, 4] and lower ones after conversion from CyA to Aza [5, 9–11]. In most studies in the past, CyA was used in high doses [9–11]. In our study, the mean serum creatinine values did not differ in recipients under triple drug treatment or any of the double drug combinations, and the group without CyA did not have lower creatinine values than the groups with CyA at 1 year. In every group the mean initial CyA dose was low and at 1 year 3.5–4.6 mg/kg. The advantage of triple drug treatment with low-dose CyA is the avoidance of cyclosporin nephrotoxicity, and in this study there were no more differences in creatinine in the long-term after CyA withdrawal compared to groups on CyA.

It is also noteworthy that grafts that were lost without the loss of the patient were distributed in two groups only, namely, in the one that continued on Aza, MP, and CyA (two lost grafts) and in the group that continued on CyA and MP (three lost grafts, one of these prior to withdrawal; the graft never functioned). It would be tempting to blame CyA for the graft losses; however, no losses were recorded in the group receiving CyA and Aza. After withdrawal, though, grafts that were lost due to death of the patient were more equally distributed, with one such case in the

group that continued on CyA and MP and four in each of the remaining groups. In the triple drug treatment group, there were three deaths due to infection but, as a matter of fact, only one of these patients was actually on triple drug treatment, two others having dropped out earlier because of azathioprine intolerance. In our study there were no more fatal infectious complications with triple drug treatment.

The highest frequency of drop-outs after conversion was recorded in the groups that continued on Aza and MP (11/28) or on Aza and CyA (8/29). This was nearly twice as high as the frequency of drop-outs in the group that continued on triple drug treatment (4/32) or on CyA and MP (4/29). On the other hand, it was not possible to withdraw medication in all patients. Nor was it possible for all patients to continue with triple drug treatment. Still, nearly twice as many drop-outs were recorded in the groups where CyA or MP was discontinued as in groups where Aza was withdrawn or triple drug treatment continued. At 1 year there was an equal number of functioning grafts in each group, but on the originally randomized medication only 14 patients in group C (Aza and MP). The reason for this was, on the one hand, azathioprine intolerance and, on the other hand, many rejections after CyA withdrawal, resulting in CyA being added again to the immunosuppression. At 1 year, 32 patients (29%) were on triple drug treatment, 41 (37%) on CyA and MP, 21 (19%) on Aza and CyA, and only 15 (14%) on conventional Aza and MP.

The complications of eliminating CyA from triple drug therapy and continuing only with Aza and MP need to be emphasized. There are many studies showing high frequencies of rejection after conversion from CyA to Aza in double drug regimens [3, 10, 11, 15], even with graft loss [3, 10]. In some studies, rejection frequency was low when steroid dosage was increased during conversion [7, 8, 14] or when conversion for first grafts was not undertaken until 1 year later [17]. We observed a 36% incidence of acute rejection after conversion in the group in which CyA was removed and a 14% incidence when steroids were removed. In our study the severity of rejections was, however, low after conversion, and no graft losses were recorded during this critical period in any one of the groups. We interpret these findings as indicating that it is too early to drop CyA routinely from the maintenance immunosuppression protocol of triple therapy at 10 weeks and/or that we removed CyA too quickly without a long enough overlapping period.

This study demonstrates that triple drug treatment with azathioprine, cyclosporin, and steroids is relatively safe to use, at least during the 1st year. Another question was whether it is necessary to continue with three immunosuppressive drugs in the long run. Withdrawal of any one of three drugs was successful in this study, and rejections, if they occurred, were mild and reversible. Finding no differences in the long-term consequences of immunosuppression during the 1st year was slightly unexpected. Therefore, this study continues. The patients have been called to the hospital at 2 years for a thorough clinical and nephrological investigation and for a core biopsy of the graft.

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