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Renal allograft immunosuppression III. Triple therapy versus three different combinations of double drug treatment: two year results in kidney transplant patients

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Abstract. A prospective randomized trial was carried out to compare the long-term effects of triple therapy based on low-dose cyclosporin A (CyA), low-dose methylprednisolone (MP) and azathioprine (Aza) with three different double drug immunosuppressive regimens. After initial triple drug immunosuppression for 10 weeks, 128 patients were randomized into four different immunosuppressive groups: one group continued with triple therapy (group A) and the three other groups were treated with different combinations of two drugs: Aza and CyA (group B), Aza and MP (group C) and CyA and MP (group D). This report presents the 2-year results. For groups A, B, C and D, graft survivals were 75%, 78%, 84% and 81%, respectively, and patient survivals were 84%, 84%, 84% and 94%, respectively. After 2 years no patient had returned to dialysis in group C compared with one to three patients in every CyA-using group. However, at the end of the 2nd year, group C included more patients with deteriorating graft function than the other groups. Median serum creatinine was 107, 120, 139 and 129 μmol/l for groups A, B, C and D, respectively. For the patients who remained on the original randomized protocol, there were no significant differences in graft function tests between the four groups, the median creatinine being 115, 115, 118 and 113 μmol/l for groups A, B, C and D, respectively. Thus, no graft deterioration had occurred during the 2 years for these patients following the original protocol. Our results suggest that after initial triple therapy, patients with a first cadaveric kidney allograft can either continue with triple therapy or be converted to any of the double drug regimens without detriment to graft function, graft survival or patient survival for the next 2 years. This will allow more flexible and individual immunosuppressive treatment.

Key words: Triple therapy, renal transplantation – Renal transplantation, double and triple therapy

The ideal combination of immunosuppressive treatment after renal transplantation is still unknown. During conventional treatment with azathioprine (Aza) and steroids, a great number of graft losses are due to acute irreversible rejection [14, 21]. Cyclosporin A (CyA) reduces the number of irreversible rejection episodes and improves graft survival rates [3, 4, 7, 11]. When CyA is used alone or in combination with steroids, the doses administered are high and cause many side effects, the most serious being nephrotoxicity, which seems to be dose-dependent.

Efforts have been made to find protocols which maintain improved graft survival rate using low-dose CyA, thus reducing the side effects. Triple therapy allows a reduction of CyA dose without loss of immunosuppressive efficacy [9, 28, 29]. Indeed, triple therapy using CyA, azathioprine and steroids allows a reduction of the dose of each drug.

Whether triple therapy is safe for long-term use, or whether any one of the double drug immunosuppressive combinations is more efficacious, are also unanswered questions. Various 'shift over' or 'conversion' studies have, therefore, been carried out, but in none of these were all possible drug combinations evaluated. Whe have performed a trial initially using low-dose CyA, low-dose steroids and Aza in combination for induction therapy. After 10 weeks the patients were randomized into four different immunosuppressive groups. One group continued with the triple therapy and the other groups were treated with different combinations of two drugs. The purpose of this trial was to compare various immunosuppressive protocols in a single-centre study with special emphasis on the long-term effects and side effects of low-dose CyA versus the other dugs. This report presents the 2-year results of the study.

Patients and methods

Patients

Between January 1986 and May 1987, 128 adult patients receiving a first cadaveric renal allograft were included in a prospective randomized trial. All patients initially received triple therapy. After 10 weeks, informed consent was obtained and the patients were ran-

Table 1. Characteristics of patients and transplants on entry. All patients received initial triple therapy immunosuppression for 10 weeks before conversion

	Group A (Aza + CyA + MP)	Group B (Aza + CyA)	Group C (Aza + MP)	Group D (CyA + MP)
Number of patients	32	32	32	32
Male/female	20/12	15/17	17/15	17/15
Age (years)	47 ± 11	49 ± 13	45 ± 12	43 ± 13
Primary renal disease (%)				
Glomerulonephritis	41	28	31	28
Diabetic nephropathy	19	16	16	34
Preoperative dialysis treatment (%)				
Haemodialysis	59	50	59	47
Peritoneal dialysis	41	50	41	53
Time in dialysis (months)	17 ± 19	12 ± 8	12 ± 8	12 ± 12
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 ischaemia (h)	31 ± 7	31 ± 7	29 ± 6	29 ± 7

Mean ± SD: all differences are nonsignificant ($P > 0.05$)

domly allocated to four treatment groups each containing 32 patients. The characteristics of patients in the different treatment groups are presented in Table 1. All patients were followed up for at least 2 years.

Initial immunosuppression and the final treatment groups

The initial 10-week tripledrug immunosuppressive treatment consisted of CyA, Aza and methylprednisolone (MP). After randomization into final treatment groups, one group continued with triple therapy (group A) and the three other groups each received one of all possible combinations of two drugs: Aza and CyA (group B), Aza and MP (group C) or CyA and MP (group D). The initial immunosuppression, changes of treatment at 10 weeks during conversion and the mean actual doses of immunosuppressive drugs at 2 years are shown in Fig. 1.

The details of initial immunosuppression and changes of treatment during conversion have been reported previously [14, 15]. Briefly, CyA was initiated at 10 mg/kg per day as an oral dose, then CyA was administered according to trough whole blood level, which was measured twice weekly during the first month, and subsequently at each routine outpatient attendance. However, the method for assessing the concentration of CyA changed. At the beginning of the study, polyclonal whole blood radioimmunoassay (RIA) was used, and after January 1988 monoclonal RIA for parent molecule was used. Aza was initiated at a dose of 2 mg/kg per day and decreased to 1 mg/kg per day on day 14. MP was initiated at 1 mg/kg per day, rapidly decreasing to 0.25 mg/kg per day on day 10.

Clinical controls at 2 years

Two years after transplantation all patients with a functioning graft were readmitted to our hospital for a 3-day check-up. Graft function tests, including serum creatinine, serum urea, serum endogenous creatinine clearance, radionuclide I^{131}-hippuran clearance (tubular function) and computer-generated serial 99m-technetium-diethylenetriaminepentaacetic acid (Tc-99m DTPA) renal scan for perfusion index (perfusion) and mean transit time, were performed [12]. Blood pressure and possible treatment for hypertension were recorded. Hyperuricaemia was defined as serum uric acid above 450 μmol/l for men and 340 μmol/l for women. Hyperkalaemia was defined as plasma potassium above 4.9 mmol/l. The lipid profiles of patients were measured and all grafts were biopsied. The results of lipid determinations and biopsies will be reported in future articles.

Cyclosporin nephrotoxicity

CyA nephrotoxicity was defined as an increase of creatinine level without signs of rejection on fine needle aspiration biopsy and a decrease in creatinine when CyA dose was reduced.

Statistical analysis

Graft and patient survivals are actual. Graft loss was defined as a return to dialysis or the death of the patient with a functioning graft. Each patient is included in the final randomization group regardless of later changes in treatment. Some results are presented only for those patients who followed the original protocol. Data are expressed as mean ± SD. Analysis of variance, Fischer PLSD, Student's *t*-test and chi-squared test were used for parametric data when appropriate, and the Mann-Whitney *U*-test for nonparametric data. Differences at the level of $P < 0.05$ were considered significant.

Results

Patients

The randomization resulted in four similar populations of patients in each treatment group (Table 1). Glomerulonephritis was the cause of renal failure in 32%, polycystic disease in 14% and pyelonephritis in 13% of patients. The overall frequency of patients with diabetes was 21%.

Graft and patient survival

Actual graft survival (GS) for groups A, B, C and D at 2 years were 75%, 78%, 84% and 81%, respectively (Fig. 2), and patient survivals (PS) 84%, 84%, 84% and 94%, respectively (Fig. 3). There were no significant dif-

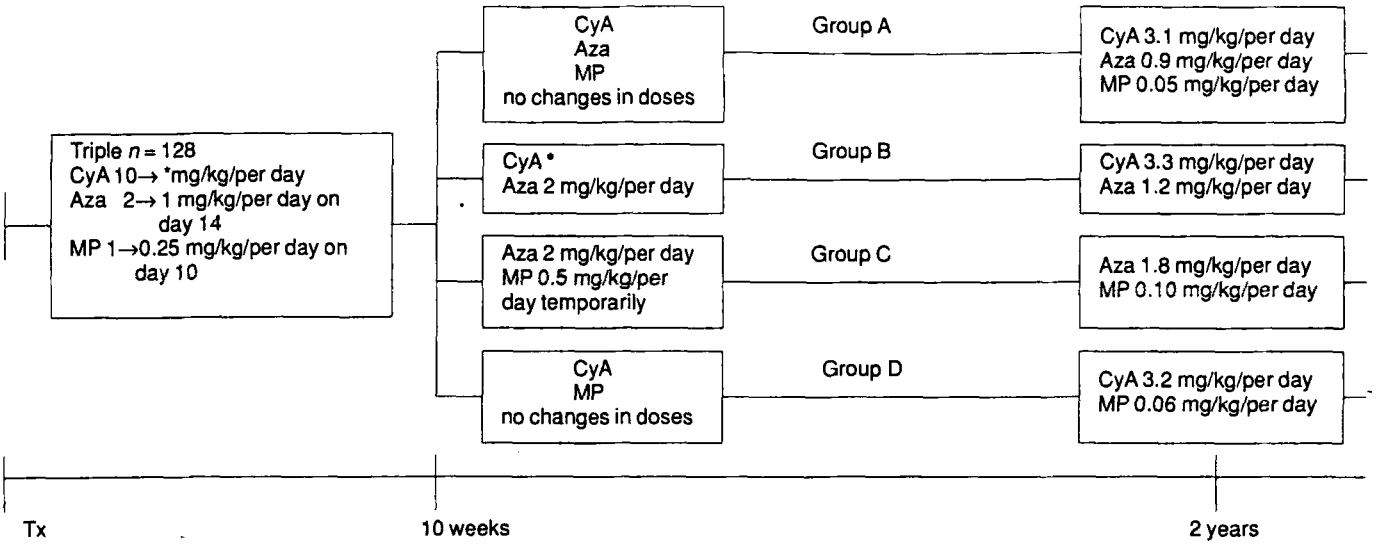

Fig. 1. *Initial immunosuppression, changes of treatment during conversion and doses of immunosuppressive drugs at 2 year for patients following the schedule.* *Cyclosporin dose adjusted to trough whole-blood concentrations. *10 weeks* = change of immunosuppression at 10 weeks during conversion; *2 years* = mean doses of immunosuppressive drugs in patients continuing on originally randomized treatment

ferences between the four treatment groups in actual GS or actual PS at any time during the 2-year follow-up. No patients were lost to follow-up.

Causes of graft and patient losses

Similar numbers of grafts were lost in each group: 8, 7, 5 and 6 grafts in groups A, B, C and D, respectively. The most common cause of graft loss was the death of the patient with a functioning graft. No graft loss occurred because of acute irreversible rejection during the 2-year period. At 2 years some patients had returned to dialysis in all groups except group C (Table 2). During the 2-year follow -up, 17 of the 128 patients died. Seven succumbed to cardiovascular complications and five to infections. There were no statistically significant differences in the causes of death between the four groups.

Graft function

Renal function tests are presented in Table 3. There were significant differences in mean serum creatinine only between group C (167 ± 73 µmol/l) and group A (123 ± 48 µmol/l), and between group C and group B (133 ± 43 µmol/l) at 2 years ($P < 0.05$). Other renal function tests in group C, i.e. endogenous creatinine clearance, urea, I^{131}-hippurate clearance and perfusion index, were also impaired when compared with the three other groups receiving CyA, but a statistically significant difference was observed only between group C and group A. Median serum creatinine was 107, 120, 139 and 129 µmol/l at 2 years in groups A, B, C and D, respectively. For patients who remained on the original therapy protocol, there were no significant differences in any graft function tests between the groups. At 2 years median creatinine for these patients was 115, 115, 118 and 113 µmol/l for groups A, B, C and D, respectively.

Change of therapy

Changes in treatment are listed in Table 2. The most common reason for a change of therapy, resulting in a drop-out from the original protocol, was azathioprine intolerance: 19% (6/32), 19% (6/32) and 22% (7/32) of patients in the groups A, B and C, respectively. During conversion at 10 weeks, discontinuation of CyA or MP was associated with increased frequency of rejections, which is the subject of a separate report [15]. This caused many drop-outs in group B and group C. Of 102 patients with a functioning graft at 2 years, 46 (45%) received CyA and MP therapy, 20 (20%) Aza and MP, 19 (18.5%) triple therapy and 17 (16.5%) Aza and CyA.

Causes of cyclosporin discontinuation

CyA was discontinued in ten cases. In two cases CyA was withdrawn during the first year and in eight patients after the first year, six because of suspicion of CyA toxicity. Two

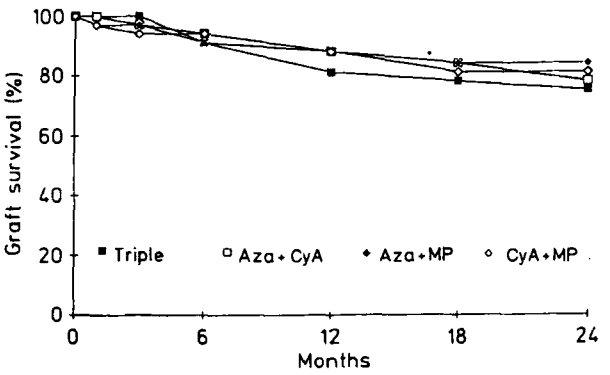

Fig. 2. Actual *graft survival* of triple therapy and different double therapy groups during the first 2 years. All differences are nonsignificant

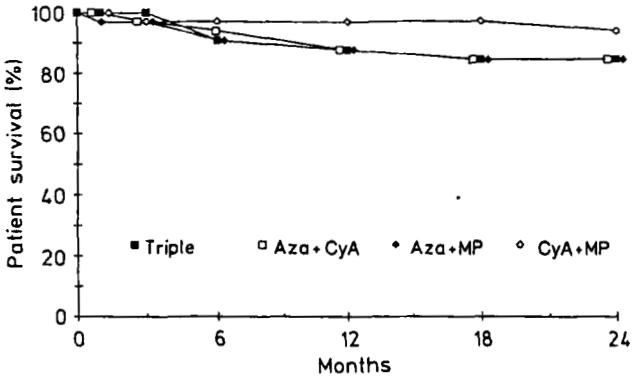

Fig. 3. Actual *patient survival* of triple therapy and different double therapy groups during the first 2 years. All differences are nonsignificant

of these six patients had clinical benefit from CyA cessation. Creatinine level decreased in one patient and another had lower blood pressure and lower serum creatinine. Two of the six patients showed no effects following the discontinuation of CyA and in two other cases the clinical situation worsened. In two cases CyA was discontinued for reasons other than toxicity.

Deterioration of graft function

At 2 years eight patients had returned to dialysis after deterioration of graft function. One of these did not receive CyA. However, all others received CyA when the deterioration of the graft function began. Four of the eight patients were on dialysis before the end of the first year. Biopsy was taken only from two grafts before entering dialysis, and from two grafts in connection with transplantectomy. All showed signs of chronic rejection. Two patients had cytomegalovirus (CMV) infection at 3 months and these grafts were lost 8 and 13 months postoperatively due to chronic rejection. One patient neglected treatment and another was suspected of noncompliance. The patients without graft biopsy did not show any clinical evidence of CyA toxicity and CyA concentrations were at the therapeutic level.

In groups A, B, C and D there were 2, 2, 10 and 7 patients, respectively, with serum creatinine over 200 µmol/l at 2 years. Between the first and second year 2, 4, 6 and 4 patients had over 15% increase in creatinine value in groups A, B, C and D, respectively. In six of these patients CyA toxicity was suspected. Consequently, CyA was discontinued in two patients and in four patients the dose was decreased. In all of these six cases creatinine decreased after changing CyA dosage. One patient showed an increase in creatinine level in connection with an infection and one patient had biopsy-proven recurrence of the original disease.

Infections

The incidence of infections did not differ significantly between the four groups. All bacterial, viral and other infections were similarly distributed in the different treatment groups. There were 47%, 56%, 43% and 59% of patients in groups A, B, C and D, respectively, who did not require admittance to hospital because of suspected infection.

Pneumonia occurred in 17 patients (13%) (6/17 had *Pneumocystis carinii* infection and no prophylaxis was used). The incidence of sepsis was 6%. There were five fatal infections, three of which were pneumonia, one septicaemia and one meningitis, and four of which occurred within the first 4 months. Clinically evident CMV infection was evident in 26% of patients showing typical fever and leukopenia, excretion of early nuclear protein into urine and a serological rise of CMV-specific IgM. Herpes simplex infection was diagnosed in 13% and herpes zoster in 5% of patients.

Blood pressure

There was no significant difference in blood pressures between the groups. The mean systolic pressure for patients following the original schedule was 140 ± 15, 140 ± 24, 145 ± 19 and 143 ± 19 mm Hg and mean diastolic pressure 82 ± 8, 83 ± 8, 85 ± 8 mm Hg for groups A, B, C and D, respectively.

Table 2. Functioning grafts and treatment at 2 years

	Group A (Aza + CyA + MP) ($n = 32$)	Group B (Aza + CyA) ($n = 32$)	Group C (Aza + MP) ($n = 32$)	Group D (CyA + MP) ($n = 32$)
Patients with functioning graft	24	25	27	26
Patients on original drug regimen	14	12	12	23
Total graft losses	8	7	5	6
Dead	5	5	5	2
Returned to dialysis[a]	3	2	0	3
Never functioning graft	0	0	0	1
Total drop-outs	10	13	15	3
Treatment changed to:				
CyA + MP	6	7	10	–
Aza + MP	3	3	–	2
Aza + CyA	1	–	3	1
Triple	–	3	2	0

[a] Grafts lost due to chronic rejection

Table 3. Renal function tests at 2 years for all patients with a functioning graft

	Group A (Triple) ($n = 24$)	Group B (Aza + CyA) ($n = 25$)	Group C (Aza + MP) ($n = 27$)	Group D (CyA + MP) ($n = 26$)
S-creatinine (μmol/l)	123 ± 48	133 ± 43	167 ± 73**	150 ± 68
Creatinine clearance ml/min/per 1.73m²	62 ± 19	57 ± 20	47 ± 17*	60 ± 24
S-urea (mmol/l)	8.0 ± 3.8	9.4 ± 3.8	11.2 ± 5.7*	9.7 ± 5.6
I^{131}-hippurate clearance (ml/min)	269 ± 77 ($n = 18$)	236 ± 52 ($n = 18$)	219 ± 52* ($n = 19$)	258 ± 74 ($n = 18$)
Perfusion index (%)	109 ± 47 ($n = 23$)	111 ± 35 ($n = 21$)	142 ± 59** ($n = 21$)	125 ± 43 ($n = 20$)
Mean transit time (min)	3.6 ± 0.9 ($n = 21$)	3.4 ± 0.5 ($n = 14$)	3.6 ± 1.0 ($n = 17$)	3.8 ± 1.1 ($n = 18$)

Mean ± SD
* Aza + MP compared with triple goup, $P < 0.05$ (Analysis of variance, Fishers PLSD test)
** Aza + MP compared with triple group, $P < 0.05$, and with Aza and CyA group, $P < 0.05$
All other differences were nonsignificant

Other biochemical parameters

At 2 years there were no differences between the four groups with regard to liver enzymes, leukocytes, thrombocytes, potassium, sodium, calcium or phosphate. Hyperkalaemia was not present but hyperuricaemia predominated in group D. The frequency of hyperuricaemia was 29%, 36%, 37% and 46% for all patients and 21%, 33%, 8% and 43% for patients following the original schedule in groups A, B, C and D, respectively.

Discussion

A main clinical concern in the use of CyA is its nephrotoxicity, which may lead to progressive and irreversible deterioration of graft function [24]. During recent years many centres have made attempts to reduce the CyA dose without weakening the immunosuppressive effect. In order to avoid CyA toxicity a number of regimens have been employed. One strategy has been an elective conversion from CyA to Aza at different intervals after transplantation, with varying degrees of success [11, 13, 22, 23, 32, 33]. Another approach has been to reduce CyA when used in combination with the other two immunosuppressive drugs. The fear of overimmunosuppression in triple therapy has resulted in protocols which withdraw one of the drugs after a fixed post-transplant period. Until recently studies have reported attempts to discontinue Aza [26], CyA [5, 35] or MP (8, 9, 25) after an initial tripledrug treatment. One study reports the results of discontinuation of Aza or alternatively of CyA after triple therapy for 4 weeks, compared with the continuation of triple therapy [2].

We have conducted a prospective randomized trial comparing triple therapy with all possible combinations of two drugs after one drug withdrawal at 10 weeks. Our study has not confirmed the fear of chronic CyA nephrotoxicity when used in low doses during a 2-year period. There is no tendency for increasing creatinine levels in patients in the different treatment groups using CyA, nor in the patients maintained on the original protocol, during the 2-year period. Similar results have been obtained by others with triple therapy [27] or with double regimens using CyA [17, 18].

One theory for the nephrotoxicity of CyA is based on the effect of impairment of renal blood flow and increased vascular resistance [6, 16]. Improvement in glomerular filtration rate and effective renal plasma flow has been shown after conversion from CyA to Aza and MP treatment at 4 months [30]. In our study, the lowest I^{131}-hippurate clearance was in the Aza and MP group, but without statistical significance. I^{131}-hippurate is excreted mainly by proximal tubules. Perfusion index increases with falling perfusion [20]. The perfusion index was highest in the Aza and MP group (142% ± 59%). There was a significant difference between the Aza and MP group compared with the triple therapy (109% ± 47%, $P < 0.05$) and Aza and CyA (111 ± 35%, $P < 0.05$) groups when we included all patients in a group, but no significant difference was observed if only the patients who remained on the original protocol were considered.

The histological criteria to differentiate between CyA nephrotoxicity and chronic rejection are not clear. In our study every group using CyA included patients on dialysis at 2 years and none was on dialysis in the Aza and MP group, but, on the other hand, there were more patients with deteriorating graft function in the Aza and MP group than in the other groups. In the second year only two patients benefited from CyA withdrawal following the impairment of graft function. With careful monitoring of CyA concentration serious nephrotoxicity seems to be avoidable in most individuals.

There were no differences in graft or patient survival between the groups. At 2 years the overall patient survival was 87% and graft survival 80%. Acute rejection was no longer the main cause of graft loss when triple therapy was used for the induction of the immunosuppressive regimen during the first weeks after transplantation when the risk of rejection is very high. Most of the grafts were lost through the death of the patient; 40% of the lost patients had type I diabetes as the cause of renal failure.

We have previously reported a low frequency of rejections using triple therapy during the first 10 weeks and an

increased frequency of mild reversible rejection associated with steroid or especially with CyA withdrawal at 10 weeks post-transplantation [15]. There was no increase in the incidence of fatal infections in immunosuppression achieved with triple therapy. Neither triple therapy nor any double drug regimen seemed to be better than another in long-term use in this respect.

CyA has been reported to cause hypertension [34], disturbances in glucose metabolism [10, 34], and hyperkalaemia [1, 3]. Our study does not support these findings. Only hyperuricaemia was noted to be more frequent among CyA-using patients as previously reported [3, 31]. In addition, it should be noted that none of the patients in the Aza and CyA group had distrubances in glucose metabolism (data not shown).

This prospective randomized trial does not prove that any one of the protocols, either triple or double drug regimen, is superior to another during a 2-year period following transplantation with regard to GS, PS or graft function. Unfortunately, the number of patients following the original protocol was low at 2 years for many reasons, and this may have influenced the results. Aza intolerance was common. The results demonstrate that triple therapy is successful immediately after transplantation when the risk of rejection is high, and this policy allows the continuation of CyA as low-dose double therapy without the risk of irreversible nephrotoxicity. CyA used in low doses does not seem to cause such frequent toxic side effects as reported for high-doses of CyA.

In conclusion, triple therapy is safe to use at least during the first 2 years after transplantation; on the other hand when the period of major acute rejection risk is past, it is no longer obligatory. Alternatives are available to modulate the immunosuppressive treatment between the triple therapy and double combinations of drugs. This allows a more individual and flexible mode of treatment.

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