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Original Article

Randomized trial of conversion from mycophenolate mofetil to azathioprine 6 months after renal allograft transplantation

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Abstract

Background. In the first year after renal allograft transplantation, triple therapy immunosuppression with cyclosporin (CsA), prednisone (P), and mycophenolate mofetil (MMF) is superior to a triple therapy treatment that includes azathioprine (AZA) instead of MMF. Whether long-term treatment with CsA-P-MMF is better than treatment with CsA-P-AZA is a matter of debate, as 3-year graft survival is similar in MMF- and AZA-treated patients. The purpose of the present study was to examine the short-term effect of changing MMF to AZA in low-risk renal allograft recipients 6 months after transplantation.

Method. This was a randomized, open-label single-centre study, recruiting 48 low risk renal allograft recipients on CsA-P-MMF therapy 6 months after transplantation, comparing the outcome with continued MMF treatment (2 g b.i.d.) (group A, $n=22$) or switching MMF to AZA (1 mg/kg) treatment (group B, $n=26$).

Results. The outcome after a 6-months follow-up of patients in group A and group B was similar. Treatment failure rates (defined as clinically diagnosed acute rejection episodes) were 4.5% in group A and 3.8% in group B. There were no patient deaths and no graft failures during the 6-months observation period. Graft function was excellent and similar in both groups.

Conclusion. Replacing MMF with AZA 6 months after transplantation in low-risk renal allograft recipients is safe and is not associated with altered graft function in the short term.

Keywords: CsA dosage; low-risk kidney transplant recipients; mycophenolate mofetil to azathioprine conversion; prednisone; short-term graft survival; six-month trial

Introduction

Several single- and multi-centre studies have shown that immunosuppressive therapy with mycophenolate mofetil (MMF) markedly reduces the rate of acute rejection episodes in the first 6–12 months after renal transplantation [1–7]. The excellent effects on the rate of acute rejection episodes are in some contrast with studies that show only a marginal effect of MMF on the incidence of chronic rejection. A 3-year follow-up of patients in European and in US multicentre studies did not reveal a significant effect of MMF on graft survival [8,9]. Thus continued treatment with MMF may not be indicated for all patients.

Based on excellent preliminary results with early conversion of MMF to azathioprine (AZA) we randomized 48 low-risk recipients of a first renal allograft 6 months after renal transplantation to continued treatment with MMF (group A, $n=22$) or to switching to AZA (group B, $n=26$). The patients were followed up for another 6 months to examine the impact of the MMF to AZA switch.

Subjects and methods

Study population

From June 1997 to July 1998, 94 adult renal transplants were performed at our centre. The standard prophylactic immunosuppressive regimen included cyclosporin A (CsA; 8 mg/kg/day), prednisone (P; 0.5 mg/kg/day), and MMF (2 g/day). The prednisone dose was gradually tapered to 10 mg/day within 6 months after transplantation. Induction with antithymocyte globulin (ATG; Fresenius; 3 mg/kg/day for 7–10 days) was used for recipients of grafts with ischaemic risk factors (older donors, prolonged ischaemia time, delayed graft function).

From the above cohort, 48 patients on triple therapy, which included CsA, P, and MMF were randomized 6 months after transplantation. Treatment groups were defined as either continued MMF treatment (group A, 22 patients), or as switching MMF to azathioprine (AZA; group B, 26 patients). Inclusion criteria were (i) stable graft function prior to randomization, (ii) satisfactory graft function (creatinine <160 μmol/l), (iii) absence of a contraindication for treatment with AZA. Exclusion criteria were (i) regrafts, (ii) sensitized patients (panel-reactive antibodies $>25\%$), (iii) history of steroid-resistant rejection episodes requiring anti-lymphocyte preparations or FK506 rescue therapy, (iv) unwillingness to participate in the study. Primary end-points

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were (i) clinically and/or biopsy-proven rejection episode within 6 months after randomization, necessitating at least steroid bolus therapy, (ii) slowly rising serum creatinine due to presumed mild rejection, necessitating a modification of MMF (group A) or AZA (group B) treatment, and (iii) side-effects due to AZA or MMF necessitating withdrawal of either immunosuppressive agent.

All patients were randomized at their routine 6 months ambulatory clinic visit. After randomization, patients were asked to either continue treatment with MMF (1 g twice daily) or to discontinue MMF and start with AZA (1 mg/kg daily) the next day. Patients in both groups then had monthly follow-up visits for the next 6 months. Steroid withdrawal was attempted 9–12 months after transplantation, provided the graft function remained stable.

Statistical analysis

Patient and laboratory data were recorded at 3-months intervals from the date of transplantation up to 12 months after grafting. Baseline recipient and donor characteristics and the laboratory data were analysed with descriptive statistics and were compared with the two-tailed *t*-test. Differences in categorical variables between the two treatment groups were analysed with Fisher's exact test. The level of significance was set at $P<0.05$.

Results

Table 1 shows that the randomization could be achieved between 6 and 7 months after transplantation.

Table 1. Patient and donor characteristics in MMF-and AZA-treated groups

	Group A (MMF)	Group B (AZA)
Number of patients	22	26
Time to randomization (days)	199 ± 39	205 ± 36
Patient characteristics		
Age (years)	45.3 ± 14.6	41.1 ± 13.1
Gender (M : F)	15 : 7	14 : 12
BMI (at 6 months)	23.5 ± 10.9	24.5 ± 3.5
Dialysis mode		
HD	16	17
CAPD	5	8
None	1	1
Mismatches (A, B, DR)	4.0 ± 1.0	3.5 ± 1.4
Transplant type		
1. CAD	20	23
1. LRD	2	3
CMV risk (D/R)		
neg/neg	1	2
neg/pos	1	5
pos/neg	10	4
pos/pos	10	15
CMV disease	5/22	6/26
Donor characteristics		
Age (years)	40.9 ± 15.1	39.5 ± 17.2
Cold ischaemia time (min)	794 ± 369	663 ± 342
Delayed graft function	4/22	5/26

BMI, body mass index; CAD, cadaver donor; CAPD, continuous ambulatory peritoneal dialysis; HD, haemodialysis; LRD, living related donor.

Table 1 also lists the basic patient and donor characteristics, which did not reveal statistically significant differences between the two treatment groups.

Table 2 demonstrates that, except for MMF and AZA, the immunosuppressive regimens were comparable between the two treatment groups. In particular, the Sandimmun Neoral® dosage as well as the CsA levels at 6 and 12 months after transplantation did not differ between the two groups, and prednisone dosage was the same in both groups. The use of ATG was less in group A patients (27 *vs* 46%, $P=0.24$).

Table 3 shows that the incidence of acute rejection episodes was low in both groups in the 12-months treatment interval after transplantation (9.1% in group A, 7.7% in group B), indicating, as anticipated, positive selection of low-risk patients with well-functioning allografts within the first 6 months after transplantation. After the randomization, only one treatment failure occurred in each group, representing a success rate of 95.5% for group A (continued MMF) and 96.2% for group B (switch to AZA). In group A one treatment failure was caused by a mild rejection episode, which was successfully reverted with steroid pulse therapy, and in group B one treatment failure was due to presumed mild rejection (slowly rising creatinine) responding favourably to a switch from AZA back to MMF. Steroid withdrawal was achieved in 27% of patients on continued MMF therapy (group A), and in 38% of patients on AZA (group B; $P=0.54$).

Table 4 demonstrates that graft function was excellent in both groups. Creatinine levels were below 130 μmol/l at 6 months after randomization in both groups. The 24-h proteinuria was also below 300 mg/day in both groups with no indication of chronic rejection.

Discussion

The lack of a clear-cut benefit of prolonged treatment with the novel immunosuppressive drug MMF, as well as its high cost, have led us to attempt to switch MMF to AZA 6 months after transplantation in low-risk renal allograft recipients. Our data clearly demonstrate that the conversion to AZA is feasible and safe. Only one out of 26 patients who were switched to AZA had to be changed back to MMF treatment due to a very mild rejection episode. This is in agreement with large multicentre studies, which demonstrate that the beneficial effects of MMF are predominantly seen in the first 6 weeks after transplantation, namely a dramatic reduction in the incidence of acute rejection episodes [1–5].

Our results need to be interpreted with caution, however. We have chosen to switch only low-risk patients to AZA treatment, i.e. patients who had a well-functioning first renal allograft without severe rejection episodes. The general applicability to patients with a higher risk, for example regrafts or patients with high panel-reactive antibodies, is certainly not

Table 2. Comparison of immunosuppressive regimens

	Group A (MMF)		Group B (AZA)	
Initial regimen at time of transplantation				
Sandimmun Neoral (mg/kg/day)	8		8	
Prednisone (mg/kg/day)	0.5		0.5	
MMF (g/day)	2		2	
ATG induction	6/22		12/26	
Maintenance regimen	6 months	12 months	6 months	12 months
Sandimmun Neoral (mg/day)	264±69	248±70	246±71	237±66
Prednisone (mg/day)	10±0	6±4	10±0	6±5
MMF (mg/day)	1795±264	1978±107	—	—
AZA (mg/day)	—	—	61±13	66±14
CsA trough level (ng/ml)	199±46	190±34	198±54	184±44

ATG, antithymocyte globulin; AZA, azathioprine; CsA, cyclosporin; MMF, mycophenolate mofetil; P, prednisone. Data are mean±SD.

Table 3. Rejection episodes, therapy of rejection episodes, and treatment failures

	Group A (MMF)	Group B (AZA)
Rejections		
0–3 months	1	2
3–6 months	0	0
6–9 months	1*	0
9–12 months	0	0
Rejection treatments (*n*; 0–12 months)		
Steroid bolus	2	2
ATG or ATGAM	0	0
FK506	0	0
OKT3	0	0
Treatment failures (*n*)	1*	1**
Immunosuppression at 12 months		
P+MMF+CsA	16	1**
MMF+CsA	6	—
P+AZA+CsA	—	15
AZA+CsA	—	10

*One treatment failure occurred in group A (a rejection episode, successfully reversed with steroid pulse treatment); **one treatment failure occurred in group B (very mild rejection, successfully treated by switching back from AZA to MMF). ATG, antithymocyte globulin; AZA, azathioprine; CsA, cyclosporin; FK506, tacrolimus; MMF, mycophenolate mofetil; P, prednisone.

Table 4. Renal function and proteinuria

	Group A (MMF)		Group B (AZA)	
Month	Creatinine (μmol/l)	Proteinuria (g/day)	Creatinine (μmol/l)	Proteinuria (g/day)
0	730±287	—	684±228	—
3	122±23	0.35±0.30	118±25	0.32±0.20
6	127±29	0.39±0.36	120±28	0.35±0.26
9	130±31	0.40±0.39	123±31	0.22±0.10
12	124±28	0.26±0.18	129±34	0.24±0.21

AZA, azathioprine; MMF, mycophenolate mofetil. Data are mean±SD.

warranted and may precipitate more serious rejection episodes. Moreover, the observation period of our patients is only 6 months, and we need to examine the long-term consequences of the MMF to AZA conversion. We anticipate, however, that MMF will only have a marginal effect on long-term graft survival when given in the chronic phase after renal transplantation, as the 3-year follow-up data of large multicentre studies did not show a clear advantage of MMF over AZA or placebo [8,9].

The CsA concentrations at 1 year were relatively high in both patient groups. It is possible that a safe switch from MMF to AZA is only possible at these CsA levels. Whether prolonged MMF treatment could give additional benefits compared with AZA, regarding for example the occurrence of skin cancer, needs to be investigated in long-term studies. What is evident from our study is that a conversion from MMF to AZA can be performed safely in low-risk renal allograft recipients. As MMF treatment is several times more expensive than treatment with AZA, this switch will obviously result in substantial savings. Long-term studies are required, however, to examine the safety and the economic implications of the MMF to AZA treatment switch.

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