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Randomised open clinical trial of conversion from mycophenolate mofetil to azathioprine in cadaveric renal transplantation

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Abstract Mycophenolate mofetil (MMF) is a powerful immunosuppressive drug with established efficacy and safety. The search for a less expensive immunosuppressive protocol has led to an open randomised clinical trial of conversion from MMF to azathioprine (Aza). A total of 28 renal allograft recipients treated with prednisone, cyclosporine, and MMF was randomised into two groups: converted (early conversion) and control (late conversion). Conversion from MMF to Aza was conducted at the end of the 4th post-transplant month in the converted group and after the 12th month in the control. During the 20-month observation period, biopsy-proven acute rejection occurred more frequently in the converted than in the control group, although the difference was not statistically significant. Early conversion from MMF to Aza increased the risk of subsequent rejection in those patients who underwent at least one episode of acute rejection prior to conversion.

Key words Immunosuppression · Renal transplantation · Acute rejection

Introduction

Mycophenolate mofetil (MMF) is a powerful immunosuppressive drug which decreases by about 50% the incidence of acute rejection in renal allograft recipients treated with cyclosporine (CsA) and prednisone compared with azathioprine (Aza) [2, 4, 8]. The main disadvantage of immunosuppressive protocols containing MMF is the cost. As the effect of the drug is expressed mostly during the first few months after transplantation, it seems reasonable to withdraw MMF and to start Aza after several post-transplant months.

Patients and methods

In an open prospective trial, renal allograft recipients who underwent transplantation in the Transplantation Institute in Warsaw were randomised into two groups: converted and control. In the converted group conversion from MMF to Aza was conducted at the end of the 4th month (early conversion), while in the control group conversion from MMF to Aza was conducted after the 12th post-transplant month (late conversion). The patients were randomised to a particular group immediately after transplantation by turn according to the transplantation order from the same donor. All patients were treated concomitantly with prednisone and CsA (Neoral). The azathioprine dose was adjusted to the patient's weight: patients weighing less than 50 kg received 75 mg; between 50 and 75 kg, 100 mg; and over 75 kg, 125 mg. CsA in the whole blood level was monitored using the fluorescent polarisation immunoassay (TDx Abbott).

Inclusion criteria were first or second renal transplant from cadaveric donor, age over 18 years, ability to take oral medication within 72 h after operation, written informed consent. Exclusion criteria were systemic infections, severe diarrhea, gastrointestinal disorders, historical PRA > 80%, malignant disorders, white blood cell count less than 2.5 G/l, hemoglobin less than 5 g/dl, pregnancy, and unwillingness to use contraception during and for 6 weeks after the discontinuation of MMF treatment.

Patient and graft survival and the incidence of biopsy-proven acute rejection (BPR) as well as graft function were monitored. Treatment failures defined as graft loss, patient death, or withdrawal from the study for other reasons were also the end-point. The protocol was approved by the ethics committee.

Table 1 Characteristics of the patients

	Converted (early conversion) ($n = 15$)	Control (late conversion) ($n = 13$)	
Sex (M/F)	11/4	5/8	NS
Age (years)[a]	43.5 ± 10.2	44.5 ± 7.3	NS
HD/CAPD	15/0	13/0	NS
Duration of dialysis (months)[b]	29.0 (14–98)	49 (9–199)	NS
EPO treatment on dialyses	10 (67%)	10 (77%)	NS
Type of transplant donor:			
• Cadaveric	15 (100%)	13 (100%)	
Previous renal transplant	2 (13%)	1 (7.7%)	NS
Induction therapy with ATG	0	1 (7.7%)	NS
Number of HLA mismatches:[a]			
• HLA A	0.7 ± 0.46	0.8 ± 0.38	NS
• HLA B	1.1 ± 0.46	1.0 ± 0.56	NS
• HLA DR	0.5 ± 0.52	0.8 ± 0.69	NS
PRA latest value (%)[b]	0.0 (0.0–10.0)	0.0 (0.0–11.0)	NS
PRA historical peak (%)[b]	3.0 (0.0–40.0)	16.0 (0.0–53.0)	$P = 0.03$
No pretransplant transfusions:	8 (53%)	5 (38%)	NS
CIT (min)[a]	2111.1 ±746.3	2022.2 ± 562.2	NS
Patients with ATN	5 (33%)	3 (23%)	NS
ATN (days)[a]	0.0 (0.0–11.0)	0.0 (0.0–26.0)	NS
Age of transplant donor[a]	37.1 ± 14.3	40.7 ± 14.9	NS
Primary renal disease:			
• Chronic glomerulonephritis	9	6	
• Chronic pyelonephritis	3	3	
• Adult polycystic kidney disease	1	2	
• Hypertensive kidney disease	1	0	
• Unknown	1	2	
CMV IgG (+)	11 (73%)	12 (92%)	NS
HBsAG (+)	0	2 (15%)	NS
HBeAG (+)	0	2 (15%)	NS
anti-HCV (+)	5 (33%)	5 (38%)	NS

[a] Mean +/- SD
[b] Median, range

Results

Twenty-eight renal allograft recipients (16 men, 12 women, aged 23–58 years) were enrolled in the study. Fifteen were assigned to the early conversion group (converted), 13 to the late conversion group (control). The characteristics of the patients are shown in Table 1. The proportions of male and female patients differed in the treatment groups, but this was not statistically significant. The incidence of BPR and the treatment failure defined as graft loss and patient death as well as withdrawal from the study is shown in Table 2. During the first 4 months after transplantation BPR occurred in 5 patients (33%) in the converted group and in 3 patients (23%) in the control group. Between the 5th and 12th months after transplantation, BPR occurred in 5 patients in the converted group (recurrent in 4) and in 1 patient in the control group. After the 20th month, BPR occurred in 1 patient in the converted group. There was one graft lost due to rejection in each group: in the 20th month in the converted group and in the 7th month after transplantation in the control group. Two patients in the control group died: one due to hepatic failure (13th month) and one for unknown reasons (3rd month). Although the total methylprednisolone (MP) dose given as anti-rejection treatment was greater in the converted group, the difference in median MP dose was not significant.

In the converted group, the incidence of rejection between 5 and 12th months postoperative positively correlated with the incidence of rejection between 0 and 4 months ($r = 0.55$).

During the entire observation period (20 months), the median serum creatinine concentrations did not sig-

Table 2 Incidence of acute rejection and treatment failure in renal allograft recipients in the early conversion (converted) and late conversion (control) groups (*BPR* biopsy-proven rejection, *MP* methylprednisolone)

	Converted (early conversion) ($n = 15$)	Control (late conversion) ($n = 13$)	
Rejection			
Patients with BPR – total	6 (40%)	3 (23%)	NS
• 0–4 months	5 (33%)	3 (23%)	NS
• 5–12 months	5 (33%)	1 (9%)	NS
Recurrent	4 (27%)	1 (9%)	NS
• 12–20 months	1 (8%)	0	NS
Rejection episodes – total	14	9	NS
• 0–4 months	8	7	NS
• 5–12 months	5	2	NS
• 12–20 months	1	0	NS
Anti-rejection treatment			
• Total MP (g)	29.0	16.5	
• MP (g) (mean ± SD)	2.1 ± 2.7	1.8 ± 3.4	NS
• ATG	0	1	NS
Treatment failures:	6 (40%)	7 (54%)	NS
Graft loss	1 (7%)	1 (9%)	NS
Death with functioning graft	0	2 (15%)	NS
Withdrawal from the study due to:			
• Rejection	2 (13%)	2 (15%)	NS
• Aza intolerance	1 (6.7%)	0	NS
• Hepatopathy	1 (6.7%)	1 (7.7%)	NS
• Other	0	1 (7.7%)	NS

nificantly differ between the groups, but did tend to increase in renal transplant recipients after the early conversion (Fig. 1).

There was no significant difference between the two groups regarding prednisone dose (Fig. 2), cyclosporine dose (Fig. 3) as well as cyclosporine through level in the 4th, 8th, 12th, 16th, and 20th months after transplantation (Fig. 4).

Discussion

Several randomised studies have established that MMF has high efficacy and safety not only in renal [2, 4–8] but also in heart [3] and pancreas [1, 7] transplantation. The search for a less expensive immunosuppressive protocol has led to a randomised open clinical trial of conversion from MMF to Aza.

We observed a higher incidence of acute rejection in renal allograft recipients in whom early (at the end of

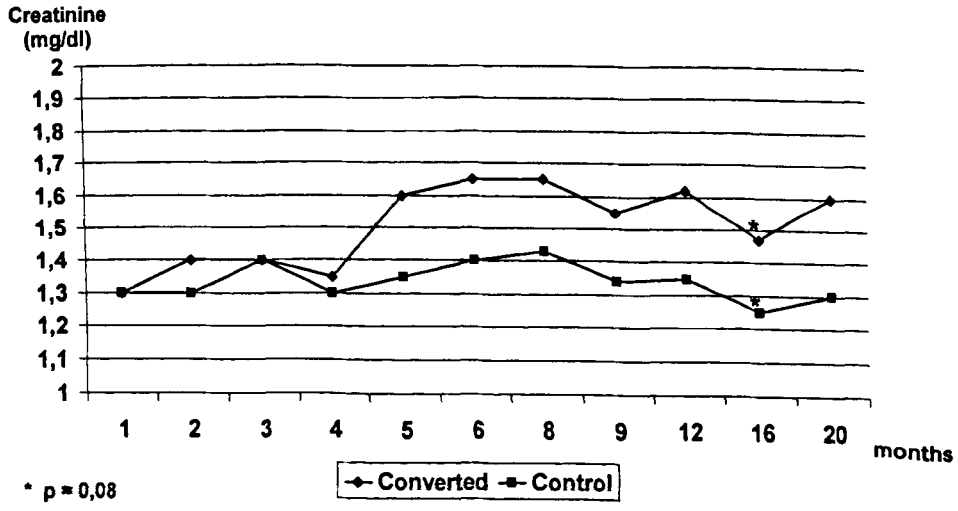

Fig. 1 Serum creatinine concentration in renal allograft recipients in the early (converted) and late (control) conversion groups (median)

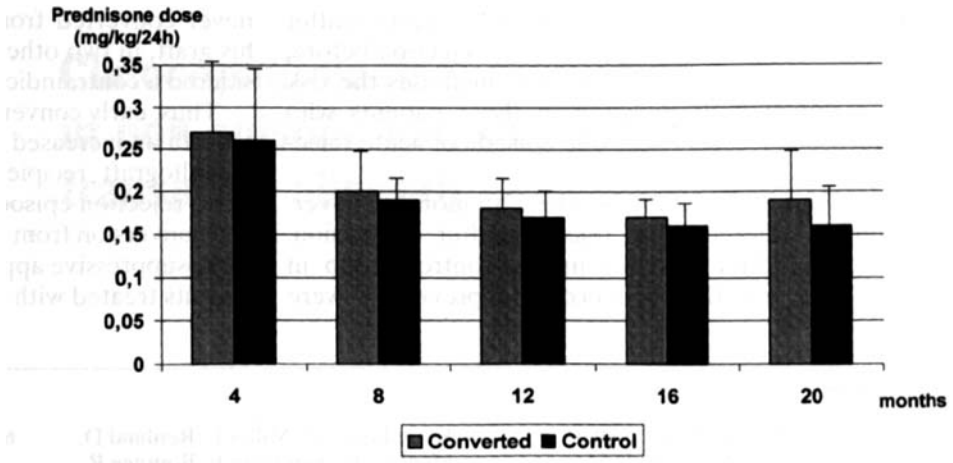

Fig. 2 Prednisone dose in renal allograft recipients in the early (converted) and late (control) conversion groups (mean + /– SD)

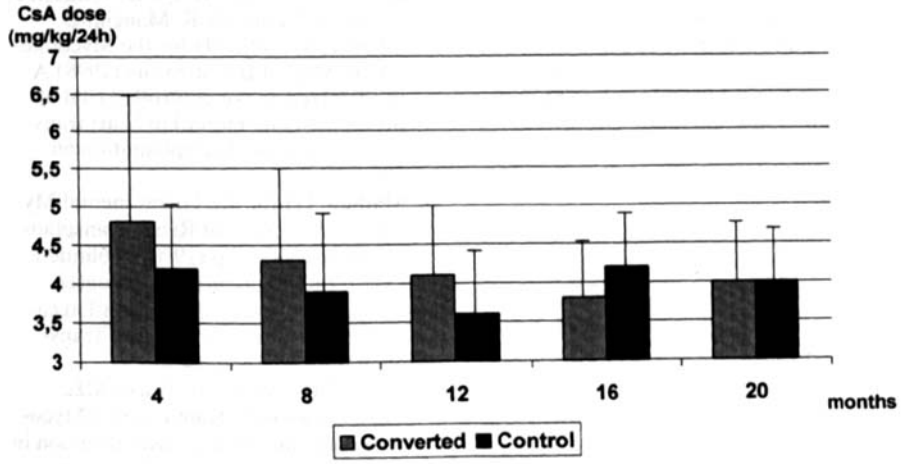

Fig. 3 Cyclosporine (CsA) dose in renal allograft recipients in the early (converted) and late (control) conversion groups (mean + /– SD)

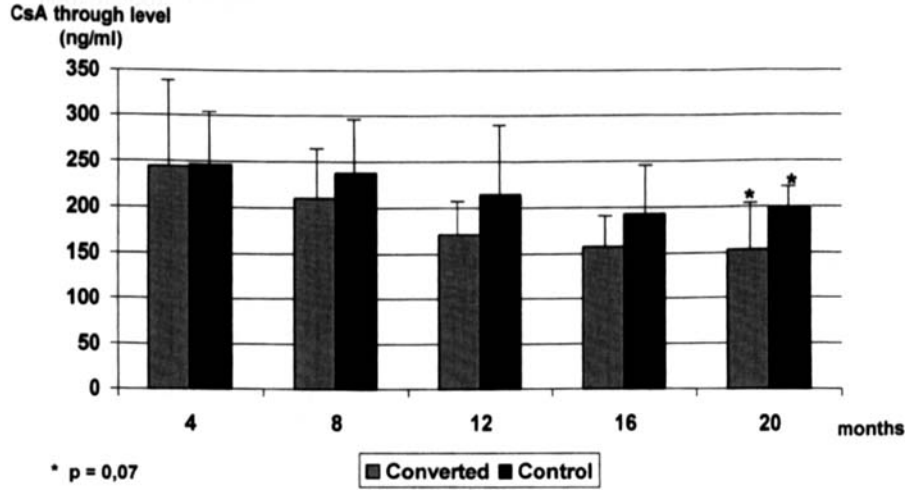

Fig. 4 CsA through level in renal allograft recipients in the early (converted) and late (control) conversion groups (mean + /– SD)

the 4th post-transplant month) conversion had been performed, although the difference was not significant. However, there was a tendency towards a higher incidence of acute rejection during the first 4 months after transplantation in the early conversion group than in the control.

Recurrent rejection was observed in 4 patients in the early conversion group. As there was a positive cor-

relation between the incidence of acute rejection after conversion and the incidence of acute rejection before, early conversion from MMF to Aza increases the risk for subsequent graft rejection in those patients who have previously had at least one episode of acute rejection.

No patient in the late (after the 12th month) conversion group suffered acute rejection after conversion. However, all three patients in the control group in whom acute rejection had occurred previously were never converted from MMF to Aza (one patient lost his graft, in two others unstable graft function was considered a contraindication for conversion).

Thus, early conversion from MMF to Aza is associated with an increased risk for subsequent rejection in renal allograft recipients who underwent at least one acute rejection episode prior to conversion. In addition, late conversion from MMF to Aza seems to be a safe immunosuppressive approach to use in renal transplant recipients treated with prednisone and cyclosporine.

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