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Conversion of stable renal allografts at one year from cyclosporin A to azathioprine: a randomized controlled study

P. Sweny, S. F. Lui, J. E. Scoble, Z. Varghese, O. N. Fernando, and J. F. Moorhead

Renal Transplant Unit, Royal Free Hospital, London, NW3 2QG, UK

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Abstract. Seventy-seven stable, nondiabetic, cadaveric renal transplants were randomized at 1 year to convert from cyclosporin A to azathioprine or to continue on cyclosporin A. Prednisolone was increased twofold during the period of conversion, and there was a 3-week overlap period during which azathioprine and cyclosporin A were given. No grafts were lost due to rejection related to conversion, but 9 of the 33 patients who were randomized to convert experienced rejection episodes and 6 were returned to cyclosporin A. Conversion to azathioprine resulted in a drop in creatinine and improvement in blood pressure control. In the group randomized to stay on cyclosporin A, 6 patients had to be subsequently converted to azathioprine because of cyclosporin A toxicity in spite of well-controlled plasma levels. The creatinine levels after successful conversion remained stable whereas those of the patients continuing on cyclosporin A showed a progressive decline. We conclude that conversion from cyclosporin A to azathioprine can be achieved safely. Progressive deterioration in graft function with continuing cyclosporin A therapy does occur and should be taken as an indication for conversion.

Key words: Cyclosporin, conversion to azathioprine – Azathioprine, conversion from cyclosporin – Conversion, cyclosporin to azathioprine

Cyclosporin A (CyA) therapy has produced an improvement in renal graft survival when compared to previous regimens [2, 3, 5, 6]. CyA nephrotoxicity has been a major problem, and studies have shown an improvement in renal function in transplanted patients previously treated with cyclosporin A and then converted to azathioprine at 3 months [4]. There have been some reports of a high incidence of rejection and of an appreciable increase in graft loss postconversion [1]. A recent large study has suggested no increased graft loss with conversion at 3 months [10], and this in spite of not using an overlap period for conversion with the first 31 patients. Another study has suggested that conversion later than 3 months confers a consistent benefit [8]. Of great concern with respect to long-term therapy with cyclosporin A is the progressive deterioration in kidney function noted in patients maintained on CyA therapy following cardiac transplantation [15]. We have sought to examine the effect of elective conversion from CyA and prednisolone to azathioprine and prednisolone at 1 year in patients whose graft function was stable and to follow such patients, comparing them with patients maintained on CyA.

Offprint requests to: J. E. Scoble

Patients and methods

From December 1983 to December 1986, 109 adult renal transplants were carried out under a standardised regimen of CyA (5–10 mg/kg per day) and low-dose prednisolone (0.3 mg/kg per day tapering to 0.15 mg/kg per day). Our aim was to keep plasma CyA levels under 150 ng/ml, as measured by HPLC. Patients with immunologically unstable grafts, i.e. frequent or late rejection episodes ($n = 2$), diabetes mellitus ($n = 3$), recurrence of their original disease ($n = 1$), a clinical indication for azathioprine (Wegener's granulomatosis, $n = 1$) or with loss of graft within the 1st year ($n = 25$) were excluded from this study. The remaining 77 patients with stable graft function were therefore randomized at 1 year post-transplantation to remain on CyA and prednisolone or to convert to azathioprine and prednisolone (conversion group). Randomization was planned for 100 patients who fulfilled the entry criteria at 12 months post-transplantation and was achieved by opening randomly mixed, sealed envelopes. Patients had been stratified into two groups for randomization, depending on whether the transplant was cadaveric or living related. No stratification for HLA matching was attempted. All patients prior to randomization were maintained on low-dose prednisolone (0.15 mg/kg per day) and CyA to maintain 12-h trough plasma levels between 75 and 150 ng/ml, as measured by HPLC assay. A full discussion about the risks of rejection versus the uncertainty of possible chronic nephrotoxicity was undertaken with patients randomized to conversion. No patients refused. Informed consent was obtained only from the conversion group, as this represented a departure from generally accepted long-term maintenance therapy.

The conversion protocol is shown in Table 1. This involved a gradual reduction in the CyA dose and gradual increases in the azathioprine dose over a 3-week period. The background steroid dose was increased twofold during this period. The azathioprine dose was adjusted if leucopaenia occurred. One year after conversion azathio-

Table 1. Protocol for converting cyclosporin A to azathioprine. Cyclosporin A and prednisolone doses are relative to the doses prior to conversion. Percentages indicate change from previous maintenance therapy

	Week 1	Week 2	Week 3	Week 4
Cyclosporin A	75%	50%	25%	Stop
Prednisolone	200%	200%	200%	Reducing course
Azathioprine	1 mg/kg	2 mg/kg	3 mg/kg	3 mg/kg

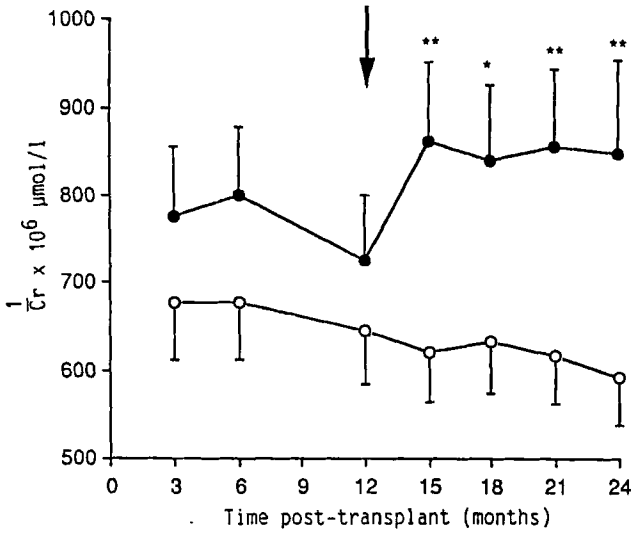

Fig. 1. Reciprocal of geometric mean ×/÷ SEM of creatinine for the conversion (●) and CyA (○) groups plotted against time from transplantation. *Arrow* indicates point of conversion to azathioprine for conversion group. * $P > 0.007$ conversion vs CyA group; ** $P > 0.002$ conversion vs CyA group

prine was reduced to 2 mg/kg per day and a year later to 1 mg/kg per day for long-term maintenance therapy. Patients who were randomized to CyA were maintained on their previous dose of prednisolone and CyA. All patients were seen twice weekly during conversion and every week for the following 6–8 weeks. Rejection episodes were diagnosed on the basis of a rise in plasma creatinine, graft swelling or tenderness. Episodes of rejection were treated with intravenous methylprednisolone (3–15 mg/kg) for 3 days. If the plasma creatinine failed to fall, then a renal biopsy was performed. Any patient with persistent rejection was returned to CyA therapy. Impairment of graft function occurring in patients not randomized to conversion was diagnosed as CyA toxicity on the basis of a renal biopsy (absent biopsy evidence of rejection or recurrence of original disease), despite acceptable plasma CyA levels. Such patients were converted to azathioprine according to the same protocol. Other causes of graft dysfunction, such as obstruction or vascular disease, were excluded by ^{99m}TcDTPA scan, intravenous urography or angiography. All patients were followed for at least 1 year postrandomization. This trial was approved by the hospital ethics committee, and informed consent was obtained for conversion.

The results are expressed as the mean ± SEM, except for plasma creatinine levels, which are expressed as the reciprocal of the geometric mean ×/÷ SEM. The mean difference was examined using an unpaired *t*-test and, if indicated, expressed as a 95% confidence interval. The percentage changes in plasma creatinine after conversion are expressed as the median and 95% confidence intervals because of nonparametric distribution. Patients in the conversion group who were returned to CyA and those not in the conversion group who were converted due to CyA toxicity were excluded from the post-conversion analysis.

Results

The data for the two groups prior to randomization are shown in Table 2 and Fig. 1. The only significant difference between the two groups was a worse mismatch at the DR locus in the CyA group. The lower plasma creatinine in the conversion group did not reach statistical significance.

In the conversion group, 9 of the 33 patients (27%) suffered a rejection episode at the time of conversion. Only four of these rejection episodes occurred within 4 weeks of the start of conversion, with three episodes occurring much later at 6, 8 and 12 weeks and two at 24 weeks. Intravenous methylprednisolone improved renal function in three of the patients with rejection, and they were maintained on azathioprine. An additional two patients responded to methylprednisolone but requested to be reconverted to CyA, and this was done. Reconversion to CyA was performed in four patients due to failure to respond to the initial course of antirejection therapy. This resulted in improvement in graft function. No graft was lost from rejection following randomization to the conversion group.

The changes in renal function, plasma electrolytes, and mean blood pressure in the groups following randomization and conversion are shown in Table 3 and Fig. 1.

Plasma creatinine levels had fallen by 15% (95% confidence intervals −10% to −20%) at 15 months in the conversion group. This improvement in renal function was maintained and was −18% (95% confidence intervals −7% to −24%) at 24 months post-transplantation. In the CyA group the plasma creatinine had risen by 10% (95% confidence intervals 2%–21%) during this period. The plasma creatinine levels were significantly lower in the conversion group at each time point at 15, 18, 21 and 24 months post-transplantation. The plasma creatinine had fallen by at least 15% in 56% of the recipients at 15, 18 and 24 months in the conversion group. There was no difference in the mean slope of the reciprocal creatinine over the first 12-month period post-transplantation between the two groups (-9×10^{-6} and -6×10^{-6} µmol/l per month for the CyA and conversion groups, respectively). However, in the conversion group, the reciprocal creatinine slope over the second 12 months was 9×10^{-6} µmol/l per month (95% confidence intervals 5–24 µmol/l

Table 2. Comparison of cyclosporin and conversion groups prerandomization

	Cyclosporin group (mean ± SEM)	Conversion group (mean ± SEM)	Significance
Number of patients	44	33	
Age	38 ± 2	37 ± 2	NS
Weight (kg)	63 ± 2	63 ± 2	NS
Mean BP at 12 months (mm Hg)	106 ± 2	109 ± 3	NS
Mismatch A (0/2)	1.3 ± 0.1	1.0 ± 0.1	NS
Mismatch B (0/2)	1.1 ± 0.1	0.9 ± 0.1	NS
Mismatch DR (0/2)	0.9 ± 0.1	0.5 ± 0.1	$P < 0.02$
Highest pre-Tx PRA (%)	10 ± 3	15 ± 5	NS
Highest post-Tx PRA (%)	22 ± 4	17 ± 4	NS
Rejection episode/patient	1.9 ± 0.2	1.5 ± 0.12	NS
Cyclosporin dosage (mg/kg)	6.4 ± 0.4	5.8 ± 0.6	NS
Cyclosporin level (ng/ml)	86 ± 4	95 ± 7	NS
Potassium at 12 months (mmol/l)	4.3 ± 0.1	4.2 ± 0.1	NS
Urate at 12 months (mmol/l)	0.54 ± 0.02	0.54 ± 0.02	NS

Table 3. Comparison of cyclosporin and conversion groups postrandomization

	Cyclosporin group (mean ± SEM)	Conversion group (mean ± SEM)	Significance
Potassium (mmol/l)			
12 months post-Tx	4.3 ± 0.1	4.2 ± 0.1	NS
15 months post-Tx	4.3 ± 0.1	3.9 ± 0.1	$P < 0.001$
18 months post-Tx	4.3 ± 0.1	4.1 ± 0.1	NS
24 months post-Tx	4.3 ± 0.1	3.5 ± 0.1	$P < 0.001$
Urate (mmol/l)			
12 months post-Tx	0.54 ± 0.02	0.54 ± 0.02	NS
15 months post-Tx	0.56 ± 0.02	0.42 ± 0.03	$P < 0.001$
18 months post-Tx	0.59 ± 0.03	0.42 ± 0.02	$P < 0.001$
24 months post-Tx	0.61 ± 0.03	0.45 ± 0.03	$P < 0.001$
Mean BP (mm Hg)			
12 months post-Tx	106 ± 2	109 ± 3	NS
15 months post-Tx	111 ± 2	102 ± 2	$P < 0.01$
18 months post-Tx	111 ± 2	100 ± 2	$P < 0.001$
24 months post-Tx	115 ± 3	105 ± 2	$P < 0.01$

Table 4. Comparison of cyclosporin patients with stable renal function and those requiring conversion for nephrotoxicity

	Cyclosporin A ($n = 38$) (mean ± SEM)	Late conversion ($n = 6$) (mean ± SEM)	Significance
Cyclosporin A level at 12 months (ng/ml)	87 ± 5	78 ± 8	NS
Rejection episodes per patient	1.9 ± 0.2	2.3 ± 0.5	NS
Plasma creatinine[a] (μmol/l)			
3 months post-Tx	137 ×/÷ 1.08	248 ×/÷ 1.07	$P < 0.001$
6 months post-Tx	138 ×/÷ 1.07	243 ×/÷ 1.08	$P < 0.002$
12 months post-Tx	152 ×/÷ 1.08	242 ×/÷ 1.10	$P < 0.006$

[a] Geometric mean ×/÷ SEM

per month, $P < 0.004$). The slope of the reciprocal creatinine over the same period for the CyA group was -3×10^{-6} μmol/l per month, but this improvement was not statistically significant. The postconversion difference between the mean slope of the reciprocal creatinine against time for the conversion and CyA groups was 12×10^{-6} μmol/l per month, $P < 0.006$. Plasma potassium and urate levels were also significantly lower in the conversion group, but there was no difference in the plasma glucose levels. At 24 months post-transplantation the mean arterial blood pressure was 10 mm Hg (95% confidence intervals 2–18) lower in the conversion group than in the CyA group. This was largely due to a steady rise in the blood pressure in the CyA group. After 24 months, 5 of the 27 patients in the conversion group had had their antihypertensive medication reduced, and in only one case was it necessary to increase antihypertensive therapy. In the 40 patients in the CyA group, 6 had their antihypertensive medication increased and 6 decreased.

Comparison between those patients who were successfully converted to azathioprine ($n = 24$) and those who had rejection after conversion ($n = 9$) revealed no difference in the degree of HLA matching, the highest pretransplant or post-transplant panel reactive antibodies or number of rejection episodes immediately post-transplant. None of the patients who had rejection episodes after conversion was a second transplant.

In the CyA group, 6 of the 44 patients (14%) required conversion to azathioprine because of progressive loss of renal function with renal biopsy findings compatible with CyA toxicity. CyA levels were within the range 75–150 ng/ml for all of the patients requiring conversion. These six patients were converted at 15, 16, 18, 18, 27 and 30 months post-transplantation. Analysis of the patients who were randomized to the CyA group but who were subsequently converted because of CyA toxicity is shown in Table 4. The six patients had lower CyA levels at 12 months post-transplant than did the patients without toxicity. They also had significantly higher creatinine levels at 3, 6 and 12 months post-transplant than patients not exhibiting toxicity. There was no significant difference in the number of rejection episodes per patient by 12 months.

One patient was lost in each group due to death from myocardial infarction.

Discussion

Although the two groups were numerically different, an interim analysis of 33 patients who were successfully converted to azathioprine and followed for at least 1 year will now be presented in light of the importance of the progressive divergence in graft function between the two groups. A total of 100 patients were recruited, but prolonged follow-up is not yet available because of a reduction in the transplant rate during 1987.

The incidence of rejection after conversion, despite an overlap and an increase in prednisolone cover during the conversion period, was still significant (27%) in a group of stable grafts and was higher than the 16% reported by Watson et al. [21]. In our study no grafts were lost due to rejection after conversion, in contrast to the Watson et al. study, where there was 7% graft loss in the conversion group. Of the nine patients who rejected after conversion, five responded promptly and completely to conventional antirejection therapy: three remained on azathioprine, but two requested to be returned to CyA therapy, which was done. Four patients responded slowly or incompletely to rejection therapy and CyA was therefore reintroduced. This illustrates the care needed in follow-up, both during and following the period of conversion. It was impossible to predict which patients were likely to reject at conversion even though unstable grafts were excluded, as it has been suggested that these have a particularly high risk of rejection at conversion [18].

This study shows that conversion at 1 year is associated with episodes of rejection; however, if this is promptly and actively treated, there is no increase in graft loss. If conversion is successful, then renal function improves and this improvement is well maintained. Specific subgroups of patients may need to stay on CyA, but these patients cannot be readily identified prior to conversion. Conversely, there is a second group of patients in whom conversion to azathioprine is necessitated because of CyA toxicity; that was the case with 6 of 44 patients in this study. This occurs despite maintenance of the generally accepted safe therapeutic blood levels of CyA. Grafts that although

immunologically stable function poorly appear to be very sensitive to CyA toxicity and would appear to benefit from early elective conversion to azathioprine. Analysis of our data failed to identify any risk factors for the group of patients who cannot be converted despite good and stable graft function.

Despite the incidence of rejection at conversion, CyA therapy may not be the preferred long-term therapy. Many trials have shown an early drop in plasma creatinine in patients successfully converted from CyA to azathioprine [7, 9, 11, 13, 14, 16, 17, 19, 20]. The recent study by Kootte et al. [12] also demonstrated better graft function in the converted group although conversion was carried out at 3 months rather than at 12 months as in our study. No grafts were lost although episodes of rejection were slightly more frequent in the conversion group in the Kootte et al. study. Our data suggest that a progressive decline in renal function occurs with continuing CyA therapy, something which is not seen with azathioprine therapy. Although the postconversion plasma creatinine was not statistically different from the preconversion level and there was no significant change in the creatinine level over the 2-year period in the CyA group, there is a divergent trend in renal function between the two groups. The slopes of the reciprocal creatinines were negative and similar in the two groups during the 1st year post-transplantation, but the slope became positive in the conversion group, indicating an improvement in renal function postconversion. This was statistically significantly different from the slope in the CyA group as were the creatinine levels at 15, 18, 21 and 24 months post-transplantation. CyA toxicity may not be fully reversible if therapy is prolonged, as has been documented in the studies of cardiac transplant patients [15]. Other reasons suggested for conversion include an improvement in urate, glucose tolerance and lipids. We have also confirmed the improvement in blood pressure control after conversion [9, 10].

Further randomized and controlled studies over a period of several years will be needed to determine whether or not long-term graft function is worse with CyA. Almost all reported studies have shown a marked improvement in short-term graft survival with CyA, but our data suggest that there may be a gradual fall-off in renal function with time in the CyA-treated group, as has been seen in cardiac transplant patients. It may well be that the graft survival figures at more than 5 years post-transplant will be worse when CyA-treated patients are compared to azathioprine-treated patients. It is important that further, larger randomized trials of conversion be conducted with long-term follow-up data on the two cohorts being reported for several years postconversion.

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