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Post-transplant conversion from cyclosporin to azathioprine: effect on cardiovascular risk profile

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Abstract. The benefits of long-term cyclosporin (CyA) therapy are not yet established and must be weighed against its toxicity. We studied cardiovascular risk factors in 25 patients who received a kidney transplant between 1985 and 1989 and in whom CyA was discontinued. The protocol for discontinuing CyA involved starting azathioprine (Aza) and then weaning CyA over 6 weeks without changing the prednisone dose. Parameters collected from the patients' charts 3 months before (pre) and 3 months after conversion (post) and at the most current follow-up (cur) included serum creatinine, cholesterol, blood pressure, and anti-hypertensive medication. The severity of the hypertension was graded, based on a hypertension index reflecting the nature and dose of the anti-hypertensive medication. Of the 25 patients in whom CyA was discontinued, 2 experienced a rejection episode during conversion and were switched back to CyA; 1 patient had a rejection episode after conversion but remained on Aza. Converted patients demonstrated improved renal function (1/Cr pre 0.69 ± 0.20, post 0.84 ± 0.23, $P < 0.05$), lower serum cholesterol levels (pre 6.8 ± 1.0, post 5.8 ± 1.2, $P < 0.05$), lower mean arterial pressure (pre 111 ± 14, post 102 ± 8, $P < 0.05$) and a lower hypertension index (pre 2.45 ± 2.77, cur 1.62 ± 1.70, $P < 0.05$). Although conversion may carry some risk of acute rejection, it improves graft function and the cardiovascular risk profile significantly.

Key words: Conversion, cyclosporin, kidney transplantation – Kidney transplantation, conversion, cyclosporin – Cardiovascular risk, conversion, cyclosporin

Introduction

Cardiovascular events are the major cause of long-term morbidity in patients with a functioning renal transplant and account for 30% of deaths in this population [8, 9, 11]. This is very likely a reflection of the accelerated atherosclerosis observed in patients who undergo prolonged maintenance dialysis [14] and of the high incidence of post-transplant cardiovascular risk factors, such as hypertension and hypercholesterolemia. Immunosuppressive therapy with cyclosporin (CyA) and prednisone has been linked to post-transplant atherogenic risk factors [8]. Azathioprine (Aza), though a less effective immunosuppressant, has no obvious atherogenic side effects [8]. Although the change from Aza to CyA maintenance therapy in the early 1980s improved early graft survival by 10%–20%, it may have increased the incidence of late cardiovascular events. In a recent review of the causes of transplant failure, it was reported that the incidence of cardiovascular death has not decreased; in fact, it showed a slight increase in the 1980s compared with the 1970s [21]. Post-transplant conversion of CyA to Aza may be considered an option for reducing cardiovascular risk factors, but the danger of developing acute rejection remains a concern. The results of many conversion trials have been controversial with some centres reporting a high incidence of acute rejection and graft loss and others experiencing no significant problems [20]. Very few of these conversion studies have dealt with side effects other than nephrotoxicity. In the present paper we review our experience with conversion from CyA to Aza immunosuppression and focus on changes in the cardiovascular risk profile.

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Patients and methods

Between May 1985 and April 1989, 123 patients received a renal transplant from a living ($n = 25$) or cadaveric ($n = 98$) donor. Initial treatment consisted of CyA at a dose of 3–4 mg/kg per day IV for the first 2–3 days, followed by 10–12 mg/kg per day p.o.. Whole blood CyA levels were measured using a radioimmunoassay kit (CYCLO-trac SP RIA kit). Methylprednisolone (1 mg/kg) was given pre-operatively and then weaned post-operatively by 10 mg/day until the patient was on 0.3 mg/kg per day of prednisone at discharge. Rejection episodes were treated with 750–1000 mg of methylprednisolone IV for 3 consecutive days; steroid-resistant rejection episodes were treated with OKT3.

Patients were followed by one of three nephrologists; patient assignment to a particular nephrologist was based on ward attendance during initial hospitalization, which was done on a rotating schedule. All patients followed by one nephrologist were converted because of hypertension and concerns regarding long-term complications. Informed consent was obtained from all patients to be converted. The conversion protocol involved starting azathioprine at 1.5–2.0 mg/kg per day, followed by weaning of CyA over a 6-week period. Data were collected retrospectively from the outpatient record 3 months before conversion (pre), 3 months after conversion (post) and at the most current follow-up (cur). Because the value of the parameters collected might possibly change over the study period as part of the post-transplant course, a cohort of non-converted, control patients on CyA and prednisone therapy, who had received a transplant in the same time period, were randomly selected. The timing of data collection in this group was based on the mean time of conversion in the study group (21 months). Therefore, data was collected at 18 months after and 24 months after (post) transplantation and again at the most current follow-up (cur). There was no dietary counseling or significant change in weight in either the control or conversion group during the study period. Rejection episodes were defined as the need to administer Solu-Medrol or OKT3 because of deterioration of graft function. Parameters collected included serum creatinine, cholesterol levels, blood pressure and the amount and nature of the anti-hypertensive drugs prescribed on clinical grounds. Blood pressure recordings were done once in the supine position. A hypertension index was calculated for each patient at the different time intervals based on the daily anti-hypertensive requirements as follows: ≤ 25 mg of captopril, ≤ 10 mg of enalapril, ≤ 20 mg of nifedipine, ≤ 90 mg of diltiazem, ≤ 5 mg of prasozin, ≤ 50 mg of atenolol, ≤ 400 mg of acebutalol or ≤ 0.3 mg of clonidine were scored 1; doses of > 75 mg of captopril, > 20 mg of enalapril, > 40 mg of nifedipine; > 180 mg of diltiazem, > 10 mg of prasozin, > 100 mg of atenolol, > 800 mg of acebutalol or > 0.6 mg of clonidine were scored 3, while intervening doses were scored 2. The scores for each of the drugs used were added to get the hypertension index. Unpaired t-tests were used to compare means unless otherwise indicated. All results are expressed as mean ± standard deviation.

Table 1. Characteristics of patients in the conversion group and the control group. NS, Not significant ($P > 0.10$)

	Control	Conversion	P value
Number of patients	23	25	
Cadaveric living related donor	17/6	18/7	NS[a]
First/second transplant	19/4	22/3	NS[a]
Sex (M/F)	13/10	10/15	NS[a]
Mean age	41.6 ± 11.4	33.2 ± 11.0	0.02
Number of mismatches			
HLA-A, B	2.3 ± 1.0	2.0 ± 1.3	NS
HLA-DR	0.68 ± 0.65	0.52 ± 0.50	NS
CyA trough level[c] (ng/ml)	165.5 ± 72.8	130.9 ± 11.3	0.08
Rejection episodes[c]	11	8	
0	7	6	
1	5	11	NS[b]
> 1			
Renal function[c] (1/μmol per liter) (1/Cr × 100)	0.72 ± 0.21	0.69 ± 0.20	NS

[a] Chi-square test
[b] Mann-Whitney U-test
[c] Before conversion or at 18 months in controls

Table 2. Effect of conversion on biochemical parameters.* $P < 0.05$ versus pre-conversion level; ** $P < 0.05$ versus pre-conversion level and versus control

	Before conversion	After conversion	At current follow-up
1/Creatinine (1/μmol per liter)			
Conversion	0.69 ± 0.20	0.84 ± 0.23**	0.91 ± 0.32*
Control	0.72 ± 0.21	0.70 ± 0.20	0.74 ± 0.28
Cholesterol (mmol/l)			
Conversion	6.8 ± 1.0	5.8 ± 1.2*	5.4 ± 0.9**
Control	6.2 ± 1.5	6.2 ± 1.5	6.1 ± 1.2

Results

The demographic characteristics and factors that may affect graft outcome in the two groups are presented in Table 1. The groups are essentially comparable with the exception of a higher mean age in the control group and a marginally lower CyA trough level in the converted group. The average degree of HLA mismatching and number of rejection episodes prior to conversion was not different between the two groups. All of the converted and non-converted patients had stable graft function at the time of conversion with serum creatinine levels less than 250 μmol/l and no rejection episodes in the previous 6 months. The mean time from transplant to conversion was 21 ± 7 months; all but two patients were converted after 1 year of CyA therapy. The mean time from conversion to current follow-up was 31 ± 15 months in the converted patients and 27 ± 12 months in the control group.

Of the 25 patients converted, 2 experienced a rejection episode and were returned to CyA therapy; one patient had a rejection episode after conversion that was successfully treated with methylprednisolone. All 3 patients with post-conversion rejection were first cadaveric transplants with one episode of rejection in the 1st year. These patients were included in the post-conversion data. No grafts were lost in either group. One patient in the converted group developed slowly progressive deterioration in renal function consistent with chronic rejection; one patient in the control group had a mild rejection episode after 21 months that was reversed with methylprednisolone.

The effect of conversion on biochemical parameters is summarized in Table 2. Patients who were converted demonstrated a significant decrease in serum cholesterol compared to their pre-conversion levels. Renal function, defined by serum creatinine, improved significantly after conversion and showed continued improvement at the most current follow-up. By contrast, the control group did not exhibit any changes in these parameters over the conversion time period. Renal function and serum cholesterol were significantly better and lower, respectively, at the most current follow-up in the converted group than in controls.

As shown in Table 3, patients who were converted from CyA to Aza had a significantly higher pre-conversion mean arterial pressure (MAP), despite their lower age, and had a lower hypertension index than the control group, suggesting poorer blood pressure control. Conversion resulted in a significant decrease in blood pressure after 3 months. At the most current follow-up, the blood pressures were not significantly different compared with

Table 3. Effect of conversion on blood pressure and anti-hypertensive medication. * $P < 0.05$ versus pre-conversion level; ** $P < 0.05$ versus control; *** $P < 0.05$ versus pre-conversion level and versus control

	Before conversion	After conversion	At current follow-up
Mean arterial pressure (mm Hg):			
Conversion	111 ± 14**	102 ± 8*	104 ± 16
Control	102 ± 10	103 ± 10	105 ± 10
Hypertension index:			
Conversion	2.45 ± 2.77	2.31 ± 2.14	1.62 ± 1.70***
Control	3.13 ± 1.59	3.06 ± 1.63	3.10 ± 1.55

either pre-conversion or non-converted patients, but the hypertension index was significantly lower in converted patients.

Discussion

Our results demonstrate that elective conversion from CyA to Aza improved the cardiovascular disease risk profile: mean serum cholesterol decreased by 20%; mean arterial blood pressure and the need for antihypertensive medication also decreased significantly. Renal transplant function also improved, as reported by others. Although conversion may increase the risk for acute rejection, this does not seem to result in increased graft loss.

Atherosclerosis is common in dialysis patients, and cardiovascular disease is responsible for many deaths in this population [4, 14]. Cardiovascular events continue to be an important cause of death even after renal transplantation [18]. The incidence of myocardial infarctions actually rises with time after transplantation, indicating that pre-transplant-acquired disease is very likely not the only explanation [8]. Even in patients without clinically apparent vascular disease at the time of transplantation, the incidence of post-transplant vascular disease is three to five times higher than expected [13]. Risk factors associated with this increase are very likely hyperlipidemia and hypertension. Elevated LDL cholesterol levels are present in about 30% of renal transplant patients treated with Aza and prednisone [12], and the use of CyA may further increase the lipoprotein levels. Raine et al. [19] reported that the LDL cholesterol levels were higher in renal transplant patients treated with CyA than in a group treated with Aza and prednisone. More convincing are investigations that avoided the confounding influences of other immunosuppressive drugs and renal failure by studying the effects of CyA on lipids in non-transplanted patients [1, 6]. Patients with amyotropic lateral sclerosis randomized to CyA had a 21% increase in total cholesterol and a 31% increase in LDL that was not seen in patients receiving placebo [1]. Likewise, in a randomized study of patients with psoriasis, CyA caused significant increases in cholesterol and triglycerides [6].

Harris et al. [7] showed that discontinuation of CyA in renal transplant patients decreased serum cholesterol by 18%, similar to the degree of cholesterol reduction in our group of patients when CyA therapy was discontinued. Although the low-density lipoprotein cholesterol subfraction is the main contributor to the association of hypercholesterolemia and increased incidence of coronary heart disease, many studies have used total serum cholesterol to establish this relationship and to investigate the efficacy of cholesterol-lowering diets or drugs on the cardiovascular risk profile [15, 17]. The combined results of 11 cholesterol-lowering trials in non-transplanted patients suggest that each percent reduction in serum cholesterol is associated with a corresponding 2% reduction in the cardiac risk profile [15]. Therefore, the 20% lowering of serum cholesterol levels, as seen in our study, would result in a 40% lowering of cardiac risk. However, it is presently not known whether lowering the serum cholesterol in renal transplant patients has a similar impact on cardiovascular risk profile in this complicated population with multiple risk factors including hypertension and diabetes.

The incidence of hypertension is higher in patients treated with CyA than in Aza-treated patients [2]. In many of these patients complicated drug therapy is required to control blood pressure, which itself may be atherogenic [5, 10]. We demonstrated that discontinuing CyA therapy is associated with a significant decrease in mean arterial pressure at 3 months post-conversion, together with a significantly lower mean hypertension index at long-term follow-up, indicating that these patients eventually required less anti-hypertensive medication. This reduction in medication may have contributed to the reduction in serum cholesterol as both B-blocker and thiazide diuretic therapy have been associated with increased serum cholesterol levels [5, 10].

Our present report demonstrates that conversion from CyA to Aza 1 year after transplantation is safe and is associated with an improvement in the cardiovascular risk profile. This favorable effect on the risk factors and further avoidance of direct CyA-related toxic damage to vessel wall cells, as shown in in vitro and in vivo animal models [3, 16, 22], may ultimately result in reduced long-term cardiovascular morbidity and mortality after renal transplantation.

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