

RENAL FUNCTION AND BLOOD PRESSURE IN HEART TRANSPLANT RECIPIENTS TREATED WITH CYCLOSPORIN A

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Summary

Cyclosporin A (CyA) is now widely used in heart transplantation. From July, 1981 to November, 1984 55 patients received orthotopic heart transplants. Two different protocols including CyA were used. Actuarial survival was 89 per cent at six months and 85 per cent at one, two and three years respectively. Creatinine rose from $117 \pm 35 \mu\text{mol/L}$ at time of surgery to $165 \pm 47 \mu\text{mol/L}$ at one year and $174 \pm 77 \mu\text{mol/L}$ at two years. Percentage of hypertensive patients increased with time reaching 50 per cent at two years. Potentially nephrotoxic antibiotics were used in eight patients. Lower doses of CyA might be required to avoid nephrotoxicity.

Introduction

Cyclosporin A (CyA), a cyclic endecapeptide of fungal origin has been used for nine years in clinical transplantation to suppress allograft rejection [1]. Nephrotoxicity represents the most frequent and clinically important complication associated with Cyclosporin A and may ultimately limit the clinical use of the drug in long-term immunosuppression [2]. However, this nephrotoxicity cannot be truly assessed in kidney transplant recipients for obvious reasons. Recent work suggests that CyA-induced renal dysfunction may also occur in cardiac transplant recipients [3-6]. Persistent elevation of blood pressure requiring intensive combination antihypertensive therapy developed within the first weeks post-transplant in 60 to 90 per cent of cardiac allograft recipients [3-5]. We therefore examined renal function and blood pressure in our department where CyA was introduced in 1981 [7].

Material and methods

Patient selection Fifty-six orthotopic cardiac transplants were performed in 55 patients between July, 1981 and November, 1984. Forty-five patients were

TABLE I. Immunosuppressive regimen

Period	July, 1981–December, 1981	January, 1982–November, 1984
Patients	10	45
Cyclosporin A	12mg/kg/day (starting day) dosage reduced to 8mg/kg/day	3.5mg/kg/day at day 2 increased progressively to 8mg/kg/day
Prednisone	360mg pre-operatively 8mg/kg/day at day 1 decreased to 1mg/kg/day at day 7 0.3mg/kg/day at 1 month 0.2mg/kg/day at 2 months	360mg pre-operatively 8mg/kg/day at day 1 decreased to 1mg/kg/day at day 7 0.3mg/kg/day at 1 month 0.2mg/kg/day at 2 months
Azathioprine	–	3mg/kg/day pre-operatively 2.5mg/kg/day for 2 days
RATG	2–3mg/kg/day for 3 days	2–3mg/kg/day for 3 days

males and 10 females. Mean age was 35.5 ± 11.3 years, range 14–57 years. Pre-operative cardiac diseases were non-obstructive cardiomyopathy in 46 cases, coronary artery disease in eight cases and systemic disease with cardiac failure in one case. The cumulative follow-up was 58.8 patient years with a maximum follow-up of 39 months.

Immunosuppression Cyclosporin A was never administered pre-operatively. Two different protocols were followed during the study period and are outlined in Table I. The first 10 patients underwent part 1 of the protocol while the last 45 patients underwent part 2. During the initial experience CyA was given according to a fixed tapering protocol with minor changes. The occurrence of renal function abnormalities required us to change the doses and to start the CyA therapy on day 2, once good post-operative renal function was established.

In the modified protocol, azathioprine was given pre-operatively and during the first two days post-operatively.

In addition, rabbit antithymocyte globulin (RATG) was given at a dosage sufficient to lower the fraction of circulating T cells (rosette method) to <2 per cent (one dose per 10kg of body weight, i.e. approximately 2–3mg/kg/day).

The diagnosis of acute graft rejection can be reliably confirmed under CyA therapy only by serial endomyocardial biopsies. The histological findings during CyA treatment were slightly different than those observed during conventional therapy. The criteria defined two types of rejection. Severe acute rejection episodes were usually treated with pulsed methylprednisolone (1g daily intravenously for three days) followed by tapered doses in five days to previous oral prednisone dose. RATG at the same dosage as post-operatively was given for three days. In the case of a mild or moderate acute rejection episode, an increased oral prednisone dose, 100mg/day for five days, was given then tapered to near previous maintenance levels for the subsequent two weeks.

Cyclosporin A dosage CyA was measured daily during the first two weeks, then twice weekly for one month, then weekly for two months and monthly thereafter. Measurements were performed in serum separated from whole blood at room temperature using reagents supplied by Sandoz Ltd. CyA dosages were adjusted on the basis of serum levels to achieve a trough level in the range of 100–200ng/ml [8]. In most patients CyA was given twice daily and levels performed four hours after administration.

Results

Survival and rejection The cumulative actuarial survival rate of these 55 patients was 92 per cent at three months, 89 per cent at six months and 85 per cent at one, two and three years respectively. Five patients died during the first two weeks due to infection (2 patients), acute cardiac failure without rejection (2 patients), and aortic rupture (1 patient). One patient died at six months from hepatitis B. Thirty-four patients survived more than six months, 25 patients more than 12 months, 16 patients more than 18 months, 10 patients more than two years and three patients more than three years.

In the 34 patients surviving for more than six months, the incidence of rejection was one episode every 10.8 patient months. Eighteen episodes of severe acute rejection were treated with pulsed methylprednisolone and 41 episodes of mild or moderate acute rejection were treated with increased oral prednisone. Five patients after a respective follow-up of six, six, 12, 18 and 30 months never had any acute rejection.

Renal function and blood pressure The creatinine levels in $\mu\text{mol/L}$ (normal range 60–104 $\mu\text{mol/L}$) and blood pressures were reported for the 34 patients surviving for more than six months (Table II). Creatinine levels increased from $117\pm 35\mu\text{mol/L}$ at the time of surgery to the second year level of $174\pm 77\mu\text{mol/L}$ ($p<0.05$). The analysis of the blood pressure revealed an increasing percentage of hypertensive patients from 12 per cent at six months to 50 per cent at two years.

In the 10 patients surviving more than two years, creatinine levels rose significantly from the pre-operative value of $102\pm 35\mu\text{mol/L}$ to $174\pm 77\mu\text{mol/L}$ at two years ($p<0.01$), while the CyA dose declined from 12.5mg/kg/day to 8mg/kg/day. The trough plasma levels were initially high ($220\pm 80\text{ng/ml}$) but declined thereafter ($130\pm 30\text{ng/ml}$ at two years).

Infection Eight patients developed severe post-transplantation infections of various origin between the first and third month. All patients received potentially nephrotoxic antibiotics over a mean period of 47 ± 15 days. None of them died and none of them had to stop the CyA therapy because of an acute nephrotoxic episode. Nevertheless, the creatinine level was significantly higher post-therapy ($200\mu\text{mol/L}$) than previously ($100\pm 20\mu\text{mol/L}$).

If one excluded these patients from the entire group of 34 patients a non-significant rise in creatinine level remained between the pre-operative period

TABLE II. Renal function and blood pressure in the 34 patients surviving more than 6 months

Time	Start	6 months	12 months	18 months	24 months	36 months
Patients (number)	34	34	25	16	10	3
Body weight (kg)	62±13	65±12	66±10	64±8	61±7	57±10
Cyclosporin A (mg/d)	520±100	486±120	500±100	525±100	500±100	560±160
mg/kg/day	8.3±2.5	7.5±0.2	7.6±0.3	8.2±0.3	8±0.3	9.7±0.3
Trough level (ng/ml)	100±50	160±75	130±60	130±50	130±30	150±30
Steroids (mg/day)	480±100	20±5	15±5	12.5±2.5	12.5±2.5	12.5±2.5
Creatinine (μmol/L)	117±35	136±75	165±57	158±50	174±77	178±88
Blood pressure						
Systolic mmHg	130±20	155±20	150±15	150±15	150±20	—
Diastolic mmHg	70±8	90±15	85±15	92±15	90±15	—
Hypertensive patients (%)	0	4	6	5	5	—
	—	12	24	31	50	—
Diuretics	34	25	16	9	3	—

of 110±25μmol/L to the one year level of 134μmol/L and the two level of 140μmol/L.

Renal histopathology Only one patient developed a severe impairment of renal function. He underwent a renal biopsy which revealed very severe interstitial fibrosis, tubular atrophy, and interstitial lymphocytic infiltration. No glomerular damage was reported.

Discussion

Experience with CyA immunosuppression in clinical cardiac transplantation now spans nearly 3.5 years. During this time CyA has clearly contributed to improved survival rates for cardiac recipients [3,4,7]. The superior survival statistics in our department compared to previous survival in patients treated with azathioprine, high doses of corticosteroids and equine anti-lymphocyte serum are dramatic. Unfortunately, toxic effects and, in particular, nephrotoxicity may hamper its clinical use even in heart transplant recipients [6].

In our series, acute nephrotoxic episodes occurred only during part 1 of the

immunosuppressive regimen with the initial use of 12.5mg/kg/day. Nevertheless no dialysis therapy was required at that time. On a long-term basis there was a progressive increase in creatinine with time. However, the changes in creatinine appeared to relate to the use of potentially nephrotoxic antibiotics as demonstrated by our eight patients. Despite very severe histological findings in one patient, the CyA associated chronic nephropathy was reversible by conversion to azathioprine.

The potential chronic nephrotoxicity of CyA was recently pointed out by Myers [6] in a selected group of 32 recipients of heart transplants who were treated for 12 months or longer with high doses of 17.5mg/kg/day. He proposed an elegant pathogenic sequence to explain the tubular and glomerular lesions: he suggested that the tubule was the primary site of injury, the nephrons with the most severely injured tubules ceased functioning and became obsolete due to focal and segmental sclerosis [9]. Such a sequence seemed not to be present in our clinical experience. Our single case did not have glomerular damage and the glomerular filtration rate was restored after conversion from CyA to azathioprine.

Is such a chronic nephropathy inevitable or possibly preventable? Our group of 26 patients receiving the same dosage of CyA but no potentially nephrotoxic antibiotics is the first step to demonstrate that CyA can prolong graft survival without severe nephrotoxicity: in these patients the pre-operative creatinine was $110 \pm 25 \mu\text{mol/L}$, at one year it was $134 \mu\text{mol/L}$, at two years $140 \mu\text{mol/L}$. The effects of potential nephrotoxicity of antibiotics in association with CyA were reported by Whiting [10].

A second and possibly related side effect of CyA therapy was the development of hypertension in almost 50 per cent of our patients at two years post-transplantation. In other series, 20 to 80 per cent were reported [3-5]. Adequate control of blood pressure has been difficult to achieve in some cases with the use of vasodilators, calcium antagonists and diuretics [5].

Immunosuppression of cardiac allograft recipients with CyA afforded distinct improvement in terms of patient survival and rehabilitation. Several side-effects such as chronic hypertension and nephrotoxicity may occur. More careful management with lower doses might be required to prevent these complications.

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