

Long-Term Results of Cyclosporine in Cadaveric Renal Transplantation From a Single Center

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SINCE THE FIRST clinical report from Cambridge in 1979,¹ cyclosporine A (CsA) has been increasingly used in organ transplantation. Its main problem in renal grafting has been nephrotoxicity. Though many reports indicate improved graft survival at 1 year,²⁻⁵ the effects of CsA on long-term function and nephrotoxicity are uncertain. We report our experience with CsA used in 222 cadaveric renal transplants between 1981 and 1985 with a follow-up period of 18 months to 5 years.

PATIENTS AND METHODS

CsA with low-dose steroids was used as the initial immunosuppression in 222 cadaveric renal transplants performed between May 1981 and December 1985 (doses given below). Twenty-one recipients were <20 years of age, eight >60 years of age, and the remaining 193 uniformly distributed between these ages. There were 166 (75%) primary grafts and 56 (25%) regrafts (45 second, nine third, and two fourth transplants). Sixteen diabetic patients received simultaneous segmental pancreas grafts. All recipients had been previously transfused and were selected on the basis of ABO blood group compatibility, negative pretransplant lymphocytic crossmatch, and the best available HLA A and B antigen match (range, 1 to 4).

From 1981 to 1984 CsA dosage was started at 15 mg/kg/d orally for the first month, which was gradually reduced to 6 to 8 mg/kg/d by 3 months. Since 1985 intravenous (IV) CsA 5 mg/kg was administered for the first two days then oral CsA at the above dosage trough levels was monitored (whole blood RIA) and dosage adjusted to achieve a level of 800 to 1,000 $\mu\text{g}/\text{mL}$ in the first month reducing to 250 to 400 $\mu\text{g}/\text{mL}$ by 3 months. All patients received prednisolone 20 mg/d initially, which was gradually reduced and then discontinued at 3

months. Episodes of acute rejection were confirmed histologically and treated with oral prednisolone 200 mg/d for three days. Patients developing recurrent acute rejection after 3 months were treated with high-dose prednisolone as above but then maintained on prednisolone 5 mg/d on a long-term basis. If a decision was made to stop CsA due to nephrotoxicity or other reasons, conventional immunosuppression of azathioprine 1.5 to 2 mg/kg/d plus long-term low-dose prednisolone was administered. Eleven transplants that failed within 24 hours due to technical reasons have been excluded.

RESULTS

Graft Survival

Overall 1-year graft survival was 77.9% (177 of 222). Actuarial survival at 2, 3, 4, and 5 years was 74.5%, 66.9%, 61.7%, and 59.4%, respectively (Fig 1). Outcome in the 56 regrafts was similar being 60.4% at 5 years. One hundred eighty-eight (84.7%) patients remained on CsA throughout the study period, whereas 34 patients were converted to conventional immunosuppression.

Conversion was undertaken because of deteriorating renal function due to nephrotoxicity in 12 patients, nephrotoxicity with rejection in 11, the development of the lymphoma/lymphocytosis syndrome in three, recurrence of original renal disease in two, and for miscellaneous reasons in six. Actuarial 5-year graft survival in converted patients was 54.9%. Serum creatinine levels in this group dropped dramatically from a median value of 500 $\mu\text{mol}/\text{L}$ (range, 187 to 1,056) to a current median value of 145 $\mu\text{mol}/\text{L}$ (range, 104 to 252) in those currently functioning. Serum creatinine in patients who remained on CsA is shown in Fig 2. Median values at 1 to 5 years are 178, 196, 198, 181, and 156 $\mu\text{mol}/\text{L}$, respectively.

Patient Survival

Twenty-two patients (9.9%) died during the follow-up period (Fig 1). Causes of death

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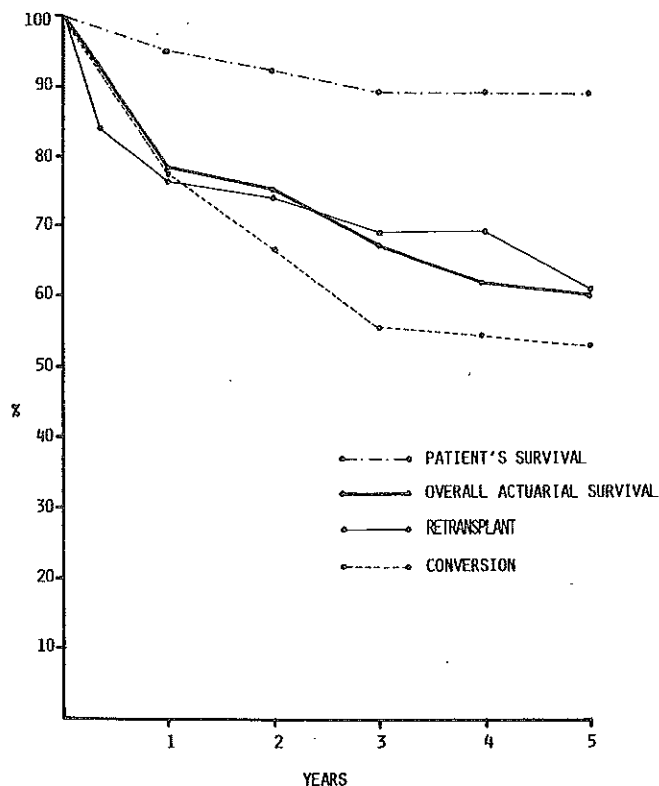


Fig 1. Patient and actuarial graft survival at 1 to 5 years.

are given in Table 1. The majority (17) died with functioning grafts. When this is added to the seven grafts lost from renal vein thrombosis and two grafts lost from recurrent disease, a total of 26 grafts (11.7%) were nonimmunologic losses.

Complications

Hypertension. At 1 year, 39 (31%) of 125 recipients with stable renal function and remaining on CsA required more antihypertensive therapy when compared with pretransplantation. Twenty-seven (59%) of these 39 patients ran serum creatinines $>200 \mu\text{mol/L}$ and 21 (54%) were still receiving low-dose steroids. In 22 recipients whose original disease was hypertensive renal failure, only four required increased antihypertensive therapy when compared with pretransplant needs.

Hyperkalaemia. Of 125 patients on CsA with stable function, 42 (33.6%) required

treatment of hyperkalaemia with bicarbonate and/or resonium (in addition to dietary control) at some stage during the first year.

Malignancy. Five patients developed the lymphoma/lymphocytosis syndrome. Conversion to azathioprine and prednisolone produced resolution in three patients but the other two patients died from the disease. One patient developed and died from metastatic lung cancer.

DISCUSSION

This series shows an encouraging long-term outcome for recipients of cadaveric renal grafts treated with CsA. A 5-year graft survival of approximately 60% with median creatinine levels of $<200 \mu\text{mol/L}$ is in keeping with earlier reports,^{6,7} and was found in both primary grafts and regrafts. Nephrotoxicity was a problem in the earlier part of the study, though it has been less of a problem since the

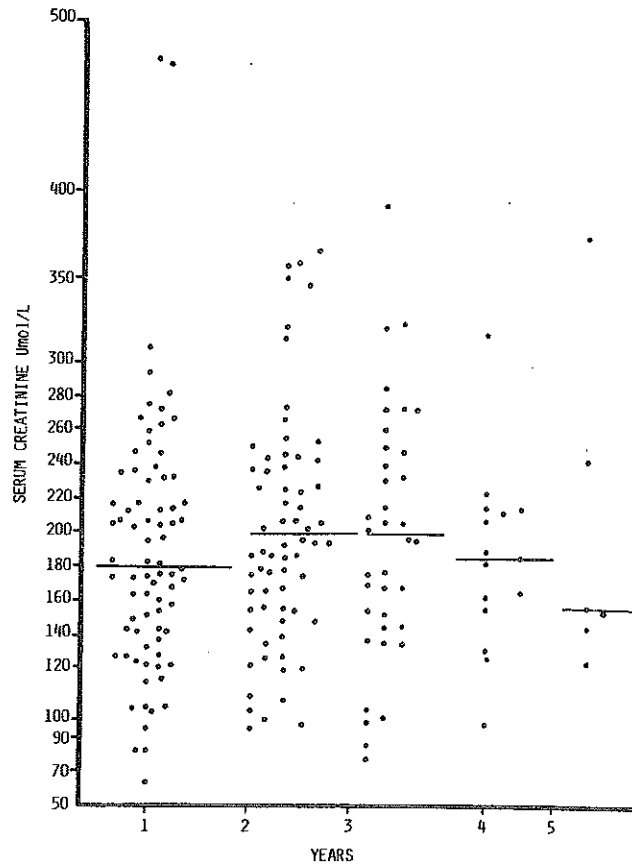


Fig 2. Serum creatinine $\mu\text{mol/L}$ at 1 to 5 years with median value (—).

development of assays to measure blood levels. Moreover, serum creatinine levels remained relatively stable during the years of follow-up (Fig 2). Significant nephrotoxicity requiring conversion to conventional immunosuppression occurred in only 10% of patients and

5-year graft survival in these was still acceptable at approximately 55% with median creatinine levels $<200 \mu\text{mol/L}$.

The incidence of hypertension in this study was less than that reported for cardiac^{8,9} and bone marrow transplant patients,¹⁰ and by other renal transplant units.^{11,12} Hypertension was more common in patients running creatinines $>200 \mu\text{mol/L}$ and requiring long-term steroids and particular care in BP control is clearly needed in this group. It is difficult to know whether any cardiovascular deaths (six in this series) could be related directly to any increase in hypertension. Though the reasons are unclear, hypertension in patients with hypertensive nephropathy was easier to control than in other recipients, and preexisting hypertension should not be considered a contraindication to the use of CsA.

Table 1. Deaths

Cause of Death*	No. of Patients
Pneumocystis	7
Other pneumonias	3
Myocardial infarction	4
Cerebrovascular accident	2
Gastrointestinal bleeding	2
Malignant lymphoma	2
Lung carcinoma	1
Perforated gall bladder	1
Total	22

*Seventeen recipients died with functioning grafts.

Hyperkalemia was seen in one third of patients but was easily controlled with resonium or bicarbonate in addition to dietary restrictions. This usually settled after the gradual reduction in CsA dosage during the initial postoperative months and was seldom a long-term problem. Lymphoma and lymphoproliferative disorders have been reported previously with CsA and steroids.^{13,14} Metastatic lung carcinoma has not been reported before with CsA and in our case this was probably coincidental lesion.

Finally, it should be stressed that most of this experience was obtained using CsA on the basis of milligram per kilogram per day and

without knowledge of blood or serum levels. Variations in absorption and metabolism are now well documented and we anticipate that better monitoring of drug levels will enable optimal immunosuppression with further reductions in side effects.

CONCLUSION

The use of CsA as immunosuppression following cadaveric renal transplantation allows good long-term graft survival (60% at 5 years) with stable graft function. Results for regrafts are not significantly different from first grafts.

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