

# Cyclosporin A in cadaveric organ transplantation

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## Abstract

The use of cyclosporin A (CyA) with a protocol designed to avoid the effects of nephrotoxicity resulted in a one-year survival of 86% in recipients of renal allografts from unmatched cadaveric donors. The drug also controlled rejection of liver and pancreatic allografts. It was possible to change patients initially treated with CyA to azathioprine and corticosteroids and vice versa, thus enlarging the potential value of CyA in organ allografting. Of 34 recipients of renal allografts, 29 were currently receiving only CyA as immunosuppressive treatment. Twelve patients never required any adjuvant steroid treatment.

These results suggest that CyA is an effective immunosuppressant, and if used with care side effects need not be severe.

## Introduction

In a pilot study of cyclosporin A (CyA) in organ transplantation we found the agent to be an extremely powerful immunosuppressant which may be effective without corticosteroids in renal, pancreatic, and hepatic allografting.<sup>1-3</sup> CyA given to 15 patients with oliguria, however, further impaired renal function, so that additional corticosteroids and "cytimun" (a cyclophosphamide analogue) were given in the mistaken belief that this was a manifestation of rejection, though histological changes did not indicate severe immune reactions. The result was excessive immunosuppression, a high incidence of bacterial, viral, and fungal infection, and the development of three lymphomas. When CyA dosage was reduced below 3 mg/kg in two patients<sup>4</sup> severe allograft rejection developed, rapidly controlled by stopping CyA and substituting azathioprine and prednisolone.

We therefore developed a protocol in which CyA was given only to patients with primary functioning kidneys. Administration of fluid and diuretics during operation lowered the incidence of primary oliguria and nephrotoxicity. The use of additional corticosteroids was limited, and if rejection was not quickly controlled CyA was stopped and immunosuppression continued with azathioprine and prednisolone. We also changed patients treated with azathioprine and corticosteroids to CyA in order to alleviate the side effects of corticosteroids.

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We report our experience with renal allograft recipients managed by the new hydration protocol, with patients whose immunosuppression was changed from or to CyA, and with patients with segmental pancreatic allografts treated with CyA.

## Patients and methods

*Group 1. Patients with kidney grafts given CyA as initial sole immunosuppressive agent*—Thirty-nine patients received cadaveric allografts. Their ages ranged from 2 to 68 years, 13 (33%) being over 50. Thirty-seven of the operations were for first grafts and two were for second, the first graft having failed for technical reasons. All patients received organs mismatched for HLA-A and B locus antigens; in most there were two or more mismatches. Details of DR matching were not available. Thirty-eight patients had had blood transfusions. Hydration began just before operation and continued in the post-operative phase, care being taken not to overload the circulation; in most cases the central venous pressure was measured. Six hours after operation, and provided that urine output was 100 ml/hour or greater, the patient began CyA, 17 mg/kg intramuscularly. As soon as fluids could be taken by mouth, usually on the second day, CyA was given as a drinking emulsion mixed with fruit juice or chocolate. After one month the dose was reduced by 2 mg/kg daily, and similar stepwise reductions were made every month until a maintenance dose of 6-8 mg/kg was reached. Allografts with deteriorating function were subjected to biopsy. Histological evidence of rejection was treated with three 1 g doses of intravenous methylprednisolone (Solu-Medrone) on consecutive days, and if improvement had not resulted during the next week the treatment was repeated. If function did not improve CyA was stopped and treatment changed to azathioprine and corticosteroids in conventional doses. If biopsy showed no rejection CyA was reduced by 30%.

*Group 2. Patients with liver or kidney grafts initially treated with or changed to CyA*—Many patients selected for liver grafting have impaired renal function, and renal failure is a common complication of operation. We used CyA as the initial immunosuppressive agent in seven patients receiving orthotopic liver grafts. A new protocol was used in 10 patients with liver allografts, in two patients who did not have a primary diuresis after renal transplantation, and in two others initially treated with other drugs. Patients were initially treated with a standard regimen of azathioprine and corticosteroids. If there was no evidence of rejection, treatment was changed to CyA 10 mg/kg/day after the 14th day, provided that the serum creatinine concentration was below 150  $\mu$ mol/l (1.7 mg/100 ml). If rejection was confirmed by biopsy while a patient was taking azathioprine and corticosteroids, the prednisolone dose was raised to 3 mg/kg and then reduced by 0.5 mg/kg every three days. When both hepatic and renal function were stable and the dose of prednisolone was 1 mg/kg or less, CyA was started, azathioprine stopped, and prednisolone reduced as rapidly as possible.

*Group 3. Patients given segmental pancreatic allografts for insulin-dependent diabetes*—Nine patients were treated with CyA as the sole initial drug. Seven received simultaneous transplantation of renal allografts from the same donor, and one a liver allograft from the same donor. The ninth patient with progressive blindness received only a pancreatic allograft. One patient developed rejection of the kidney that could not be controlled by CyA and was changed to azathioprine and corticosteroids.

## Results

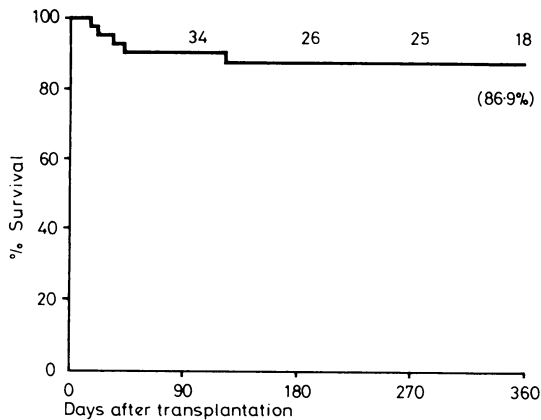
*Group 1*—Of the 39 kidney allograft recipients treated with CyA, two died from sepsis and one from haemorrhage after renal biopsy (figure). Two allografts were removed, one for local wound sepsis and the other for uncontrollable rejection. The remaining 34 grafts continued to function for two years to two months, 12 without the

need for additional corticosteroids. Seventeen patients were treated with corticosteroids for rejection episodes, but these drugs were later stopped, so that 29 of the 34 patients were no longer taking them; five patients were converted to azathioprine and corticosteroids with satisfactory control of rejection and good function in the transplants.

**Group 2**—Five of the seven patients initially treated with CyA had functioning liver allografts at 6-13 months (table I). One died at three weeks in acute heart failure, and two developed severe renal failure requiring dialysis. CyA was stopped: one patient rejected the liver

and died; the other was given azathioprine and corticosteroids and was changed back to CyA when renal function recovered. Three liver and two kidney graft recipients were converted to CyA as a deliberate policy as soon as allograft function was stable. Seven patients with liver transplants and two with kidney transplants were converted to CyA between three months and three years after operation. One of the patients with a renal allograft was started on CyA, cytimun, and prednisolone and continued with CyA alone. The other, given three months' treatment with azathioprine and prednisolone, developed bilateral hip arthritis requiring six weeks of traction. He was last being treated with CyA; azathioprine had been stopped and prednisolone was being slowly withdrawn. After conversion, allograft function continued with little change in all cases.

**Group 3**—Of the nine patients given segmental pancreatic allografts, two died, one on the fourth day from overhydration causing acute cardiac failure, and the other from septicaemia (table II). Two patients had their allografts removed for rejection; in both cases rejection was first observed clinically by deteriorating renal function, and peripancreatic sepsis occurred, with leakage of exocrine secretion. One of these patients was given a second kidney transplant and treated with azathioprine and corticosteroids; the other received dialysis. Both were taking insulin. A further patient developed uncontrollable rejection of the kidney 70 days after operation, and immunosuppression was changed to azathioprine and corticosteroids. Renal function was restored but the use of corticosteroids necessitated the reintroduction of insulin. The remaining four pancreatic allografts were functioning. The patients did not require insulin or corticosteroids, two (one with a kidney transplant, and one with a liver transplant) after more than a year, one at six months with a kidney transplant, and one at three months without any other organ graft. Renal function deteriorated in the last patient after pancreatic grafting and he required dialysis, but results of renal function tests returned to preoperative values after a reduction in CyA dosage.



Actuarial survival of 39 cadaveric kidney allograft recipients immunosuppressed with cyclosporin A. Figures on plot are actual numbers of survivors. (Calculated by method of Kaplan and Meier.<sup>12</sup>)

TABLE I—Details of 14 patients converted to cyclosporin A (CyA)

Case No	Age and sex	Reason for transplantation, and organ transplanted	Days after operation of conversion to CyA	Current graft survival (days)	Current graft function (serum concentrations)			Prednisolone dose (mg/day)
					Bilirubin ( $\mu\text{mol/l}$ )	Urea (mmol/l)	Creatinine ( $\mu\text{mol/l}$ )	
1*	47 M	Sclerosing cholangitis. Liver	30	158	20	14.4	166	0. Stopped 6/7/80, 11 days after starting CyA
2*	29 F	Cholangiocarcinoma. Liver	31	81	26	5.0	60	12.5
3*	42 F	Primary biliary cirrhosis. Liver	47	73	150	4.5	48	30
4*	19 F	Pyelonephritis. Kidney	25	49	21	31.6	304	12.5
5*	40 M	Chronic renal failure ?cause. Kidney	25	42	13	14.4	192	30
6	24 F	Budd-Chiari. Liver	132	205	19	5.9	61	8
7	55 M	Primary biliary cirrhosis. Liver	1372	1441	100	11.7	132	15
8	52 F	Primary biliary cirrhosis. Liver	1295	1332	40	6.0	96	7
9	59 M	Primary biliary cirrhosis. Liver	968	1052	19	11.6	266	0
10	27 F	Chronic active hepatitis. Liver	493	529	12	4.0	78	5
11	49 F	Polycystic kidney. Kidney	0	756	10	11.1	147	0 from 11/2/79
12	37 M	Glomerulonephritis. Kidney	88	170	12	12.2	304	0 from 20/9/80, 41 days after starting CyA
13	43 M	Secondary biliary cirrhosis. Liver	1434	1451	26	7.3	100	7
14	35 M	Hepatoma. Liver	1748	1765	12	8.6	87	6

\*Cases 1-5, new protocol: starting with azathioprine and prednisolone; changing to CyA when allograft function stable.

Conversion: SI to traditional units—Bilirubin:  $1 \mu\text{mol/l} \approx 0.06 \text{ mg/100 ml}$ . Urea:  $1 \text{ mmol/l} \approx 6 \text{ mg/100 ml}$ . Creatinine:  $1 \mu\text{mol/l} \approx 0.01 \text{ mg/100 ml}$ .

TABLE II—Details of nine patients with segmental pancreatic grafts

Case No	Age and sex	Other organ grafted	Days of pancreatic graft survival	Graft function (serum concentrations)				Insulin requirement	Observations
				Bilirubin ( $\mu\text{mol/l}$ )	Urea (mmol/l)	Creatinine ( $\mu\text{mol/l}$ )	Glucose (mmol/l)		
15	55 F	Kidney	> 439	15	11.7	155	5.9	0	Treated with CyA* only
16	25 M	Liver	> 394	40	20.0	266	4.3	0	Was on prednisolone for hepatitis. Stopped on day 254
17	47 F	Kidney	3	—	—	—	—	—	Died on day 3 from acute congestive cardiac failure due to fluid overload
18	43 M	Kidney	11	—	—	—	—	—	Rejected kidney and pancreas. Pancreas removed 5/11/79. 2nd renal allograft 29/12/79. On azathioprine and prednisolone
19	37 M	Kidney	> 250	12	9.0	188	7.5	0	Rejection of both grafts reversed with course of methylprednisolone
20	32 M	Kidney	71	—	—	—	—	—	Died on day 71 of sepsis after rejection of both grafts
21	38 F	Kidney	> 186	6	18.9	208	3.3	16 units twice daily	Persistent rejection failed to respond to course of methylprednisolone. CyA stopped on day 125. Azathioprine 50 mg, prednisolone 30 mg
22	36 M	None	> 131	68	27.0	278	3.8	0	Renal failure after pancreas grafting. Required dialysis. Return to preoperative renal function
23	45 M	Kidney	50	—	—	—	—	—	Rejected kidney despite methylprednisolone course. Peripancreatic sepsis with exocrine fistula. Both grafts removed on day 50. On dialysis

\*Cyclosporin A.

Conversion: SI to traditional units—Bilirubin:  $1 \mu\text{mol/l} \approx 0.06 \text{ mg/100 ml}$ . Urea:  $1 \text{ mmol/l} \approx 6 \text{ mg/100 ml}$ . Creatinine:  $1 \mu\text{mol/l} \approx 0.01 \text{ mg/100 ml}$ . Glucose:  $1 \text{ mmol/l} \approx 18 \text{ mg/100 ml}$ .

## Discussion

With this protocol the results obtained with CyA in patients given cadaveric renal allografts were very much better than we had obtained before. Though selected for primary function (but not immunologically), these patients (one-third of whom were over 50) have an 86% predicted graft survival at one year, which is unusual. They included five patients in whom CyA did not control rejection and who were changed satisfactorily to azathioprine and corticosteroids.

Starzl *et al* suggested that corticosteroids should be used routinely in addition to CyA.<sup>5</sup> Since three-quarters of our patients with functioning renal allografts were receiving CyA only and nearly a third had never been treated with corticosteroids, we think that patients should be given the chance to avoid the latter drugs. Early experience with continuous administration of corticosteroids with CyA<sup>2</sup> was associated with a high incidence of infectious complications and lymphomas. With the new protocol there were no new cases of lymphoma, and probably the development of such tumours is not specifically related to CyA but to excessive and inappropriate immunosuppression.

Nephrotoxicity has been the most serious complication of CyA. Other side effects have been growth of soft, downy facial and body hair, gum hypertrophy, tremor, mild hepatotoxicity (usually manifested by slight derangement of liver function values), and subclinical marrow depression. Two cases of benign mammary fibroadenomas have occurred.<sup>4</sup>

Though we and Starzl *et al*<sup>5</sup> have reported good results using CyA as an initial immunosuppressive drug in liver allografts, two of our patients developed renal failure which may have been aggravated by CyA, and we now start CyA only when the patient is stable. Initial results have been satisfactory and we have extended this regimen to patients excluded from initial immunosuppression with CyA for renal allografts because of primary oliguria. We have also converted to CyA transplant recipients who have developed side effects from corticosteroids; follow-up is short, but it is already clear that hepatic and renal function can be satisfactorily maintained.

Transplantation of the pancreas has been undertaken because of the powerful immunosuppressive effect of CyA, which can in some cases control rejection without the need for corticosteroids. Attempts to prevent exocrine secretion by injecting latex into the pancreatic duct<sup>6,7</sup> have not always been successful, and infection is likely to be aggravated because latex is a foreign body. We propose in future to inject the ducts with Ethibloc, a polymerised amino-acid, which is broken down in the body.<sup>8</sup>

The future of segmental pancreatic allografting depends on whether control of diabetes can prevent progression of microangiopathy and therefore deterioration of vision and renal function. It would then be an attractive treatment for certain patients with complicated diabetes.

CyA is effective in clinical organ and marrow allografting.<sup>9</sup> The limited information on its pharmacokinetics (M Lemaire and G Gsell; G Maurer and E Schreier; and T Beveridge *et al*—all unpublished) makes it difficult to use in practice. Control of rejection and prevention of nephrotoxicity can be achieved by monitoring blood concentrations using a radioimmunoassay and modifying the dose to maintain a trough concentration of 200–400 µg/l.<sup>10</sup> Unlike the oral preparation, CyA administered intramuscularly fails to provide significant (<50 µg/l) blood concentrations as measured by radioimmunoassay, but more data are required before drawing conclusions on the clinical relevance of blood values.

We were surprised how often renal allograft rejection not controlled by CyA responded to azathioprine and prednisolone.

This may have been due to different mechanisms of action or to variation in absorption or metabolism of CyA in different patients. Patients experiencing side effects with corticosteroids have responded well to CyA. Patients receiving CyA should not be given prolonged courses of corticosteroids or other immunosuppressive agents because of the danger of excessive damage to the immune system, with the attendant risks of infection and lymphoma induction. Thus we find that patients treated with CyA alone are capable of producing a more vigorous humoral response, as assessed by immunoglobulin concentrations, than are those treated with CyA and corticosteroids or conventional immunosuppressive agents.<sup>11</sup>

The ease with which patients may be changed to and from CyA provides a valuable alternative immunosuppressive tool. As maintenance treatment CyA is usually preferable, since corticosteroids can be avoided. Serum creatinine concentrations, however, are higher (208 µmol/l (2.4 mg/100 ml) at six months) than with conventional drugs (114 µmol/l (1.3 mg/100 ml) at six months). When patients are changed to azathioprine and prednisolone, serum creatinine concentrations usually fall rapidly, but such changes have been necessitated by poor control of rejection, and improvement in renal function may be due to recovery from rejection as well as to stopping the nephrotoxic CyA. Change to CyA in the absence of rejection is usually followed by a rise in serum creatinine concentrations, which tend to peak and then fall to remain moderately raised.

Our results are encouraging, and a randomised multicentre trial is now planned to compare CyA with conventional azathioprine and corticosteroids in recipients of cadaveric renal allografts.

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