Transpl Int (1993) 6: 223–225

Transplant International

Is there an optimal time for the first cyclosporin dose in renal transplantation?

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Received: 18 August 1992/Received after revision: 26 November 1992/Accepted: 11 December 1992

Abstract. It is customary for patients undergoing kidney transplantation to receive their first dose of cyclosporin either just before or during the transplant operation. This ensures the early establishment of good levels of immunosuppression but might depress early graft function and contribute towards the development of acute tubular necrosis. In a controlled clinical trial, we have studied the effects of withholding cyclosporin for 12 h in patients undergoing cadaveric renal transplantation. Consecutive adult recipients of a cadaveric renal transplant were randomised to receive their first dose of cyclosporin (10 mg/kg p.o.) 6 h prior to transplant surgery or 12 h afterwards. All patients received azathioprine (1.5 mg/kg i.v.) and methylprednisolone (0.5 g i.v.) in addition during surgery. From the 2nd day onwards both groups were treated with an identical triple immunosuppressive regimen. The 27 patients who received their first dose of cyclosporin post-operatively had significantly better immediate and subsequent function than did the 26 patients who received their cyclosporin at the time of surgery. The delayed dosing was associated with improved graft survival and no increase in the frequency of rejection episodes. This regimen is recommended for all patients receiving triple therapy.

Key words: Cyclosporin, renal transplantation, time first dose – Renal transplantation, cyclosporin, time first dose – Time first dose, cyclosporin, renal transplantation

Introduction

During the last 10 years, cyclosporin (CyA) has become the principle immunosuppressive agent used for kidney transplantation and it has undoubtedly contributed greatly to the improved results [4]. Unfortunately, CyA produces some adverse effects, principally nephrotoxicity [1], which may promote early renal shutdown, particularly when high-loading doses of CyA are used [2]. To overcome this problem and yet retain maximal immunosuppression early in the post-transplant period, a sequential therapy protocol can be employed. This comprises an induction period of 10–14 days during which ATG or OKT3 is given whilst CyA is withheld. Such regimens have become popular, particularly in the United States [5].

When using CyA in protocols that do not involve ATG or OKT3, it is usual practice to administer the first dose of CyA close to the time of transplantation, if not just before. This practice is supported by early in vitro work that showed that CyA was effective in suppressing lymphocyte

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Table 1. Distribution of relevant recipient factors in the two study groups

	Group 1 ($n = 26$)	Group 2 ($n = 27$)
	Pre-operative	Post-operative
Male/female	16/10	16/11
Age (years)	45 ± 12.5	43 ± 12.3
First/second grafts	24/2	24/3
HLA mismatches:		
AB	2.3 ± 1.1	2.2 ± 1.0
DR	0.8 ± 0.6	0.6 ± 0.6
Patients transfused	9	11
Dialysis:		
Haemodialysis	15	18
Peritoneal	11	8
No dialysis	0	1
Ischaemia:		
Initial (min)	6.3 ± 1.6[a]	0.04 ± 0.1
Operative (min)	36 ± 12.7	33 ± 9
Total (h)	21 ± 6.2	23 ± 7
Panel reactive antibodies:		
Maximum (%)	6.2 ± 12.0	7.7 ± 19
Current (%)	1.1 ± 4.2	2.5 ± 9

[a] One kidney with a long initial warm ischaemia time

Table 2. Distribution of relevant donor factors in the two study groups

	Group 1 ($n = 26$)	Group 2 ($n = 27$)
	Pre-operative	Post-operative
Male/female	9/17	17/10
Age (years)	42.8 ± 16.3	41.6 ± 15.9
Hypotension:		
No. hypotensive	16	16
Mean BP mm/Hg	74/44	68/36
Urine output:		
Last 1 hour (ml)	150 ± 95	144 ± 101
Last 24 hours (ml)	3315 ± 1431	3533 ± 1395
Plasma creatinine μmol/l	109 ± 43	104 ± 33
Local/shipped	19/7	14/13
Multiple arteries	3	5
Cause of death:		
Cerebrovascular	11	8
Subarachnoid bleed	8	8
Head injury	7	9
Tumour	0	2

Table 3. Post-transplant renal function and rejection episodes

	Group 1 ($n = 26$)	Group 2 ($n = 27$)
	Pre-operative	Post-operative
Immediate function	11	20 $X^2 = 5.50$, $P < 0.02$
Delayed function	11	6
Never functioned	4	1
Rejection episodes/ patient	0.7 ± 1.1	0.5 ± 0.6
Methylprednisolone (mean g/patient)	0.8 ± 1.3	0.7 ± 0.9
OKT3/ATG (patients treated)	4	1
Plasma creatinine (μmol/l) at:		
1 month	219 ± 117	169 ± 56
3 months	191 ± 49	160 ± 58 $P = 0.05$
6 + months	181 ± 19	145 ± 9

Table 4. First rejection episodes

Outset of rejection	Group 1	Group 2	
Day	18 ± 12	14 ± 14	NS
Cyclosporin level (ng/ml)	220 ± 80	204 ± 90	NS

proliferation only when added early to mixed lymphocyte cultures [3].

Triple therapy comprising CyA, azathioprine and prednisolone is commonly employed in human kidney transplantation. It is usual practice to start all three agents at the time of transplantation, often during surgery.

We have considered delaying CyA dosing for 12 h in order to encourage better immediate renal function. In the absence of ATG or OKT3, such a regimen might allow rejection to develop early. On the other hand, the azathioprine and prednisolone given during surgery could provide sufficient immunosuppression to prevent this. To investigate this further, we have conducted a small randomised controlled trial in patients receiving cadaveric renal transplants.

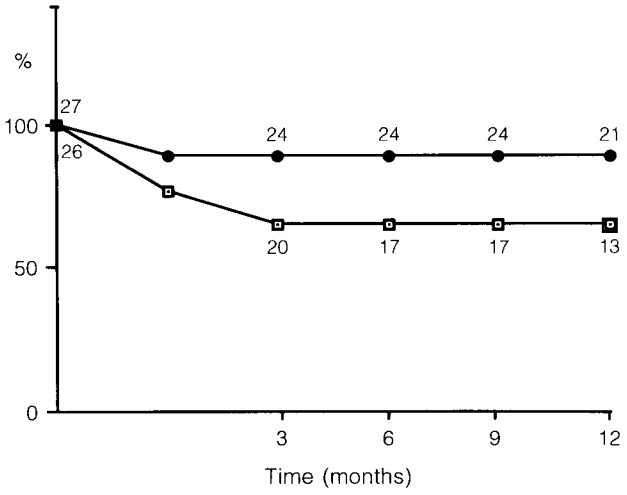

Fig. 1. Actuarial graft survival rates for the two study groups. Losses from all causes are included; all patients were followed for more than 6 months. The differences in transplant survival are not significant ($P = 0.13$). □ Pre-operative cyclosporin, ● post-operative cyclosporin

Patients and methods

Between 29 March 1991 and 12 February 1992, patients undergoing cadaveric renal transplantation were randomised to receive CyA (10 mg/kg p.o.) either 6 h pre-operatively or 12 h post-operatively. Excluded were highly sensitised patients (PRA > 80%) who received sequential therapy. Per-operative immunosuppression was with azathioprine (1.5 mg/kg i.v.) and methylprednisolone (500 mg i.v.).

Following randomisation, the junior medical officer gave the first dose of CyA to the patient at the appropriate time, but this information was not disclosed to the senior staff, who were unaware as to which group each patient belonged. Maintenance immunosuppression was with CyA, maintaining whole blood levels at 150–250 ng/ml (monoclonal-specific RIA), azathioprine (1.5 mg/kg) and prednisolone (0.3 mg/kg).

Rejection episodes were treated with daily pulses of methylprednisolone (500 mg × 3). Patients failing to respond received OKT3 (2.5–5 mg) daily for 10 days.

Results

Fifty-three patients entered into the trial – 32 males and 21 females – with a mean age of 44 years. There were 48 first cadaveric grafts and 5 regrafts. The first dose of CyA was given pre-operatively to 26 patients (group 1) and post-operatively to 27 patients (group 2). With regard to the patient's sex, age, HLA mismatching, transfusion history, method of dialysis, ischaemic time and panel reactive antibodies, both groups were well matched (Table 1). Relevant donor factors were also equally represented, although there were more imported kidneys in group 2 (Table 2).

In group 1, 11 kidneys functioned immediately (at least 10% spontaneous drop in serum creatinine over the

Table 5. Immunosuppression. CyA, Cyclosporin; Pred, prednisolone

	Group 1			Group 2		
	CyA Level (ng/ml)	CyA Dose (mg/day)	Pred (mg/day)	CyA Level (ng/ml)	CyA Dose (mg/day)	Pred (mg/day)
0		730 ± 162	21 ± 3		683 ± 145	21 ± 3
2 weeks	213 ± 56	630 ± 270	19 ± 5	200 ± 80	584 ± 254	20 ± 3
1 month	212 ± 80	510 ± 195	20 ± 5	223 ± 68	522 ± 214	20 ± 3
3 months	160 ± 45	407 ± 143	14 ± 3	183 ± 49	382 ± 114	14 ± 3
6 months	189 ± 52	335 ± 115	10 ± 3	171 ± 35	354 ± 109	10 ± 3
9 months	169 ± 85	373 ± 144	9 ± 5	183 ± 70	346 ± 103	10 ± 3
1 year	138 ± 53	432 ± 132	9 ± 3	178 ± 38	322 ± 106	9 ± 3

first 24 h). Eleven other kidneys had delayed function and 4 kidneys never functioned. In group 2, 20 kidneys functioned immediately, 6 had delayed function and 1 never functioned. Significantly more kidneys functioned immediately in this group ($X^2 = 5.505$; $P < 0.02$).

In those patients with delayed function, the mean number of haemodialyses in group 1 was 4.4 ± 3.3 (ten patients) and in group 2 it was 5 ± 1.4 (five patients). Four patients in group 1 were dialysed with CAPD. The mean period of delayed function was 13.5 ± 7.3 days in group 1 and 12.8 ± 7.3 days in group 2. However, subsequently, mean plasma creatinine levels were lower in group 2 at each time period studied, significantly so at 3 months. Delayed administration of CyA did not result in more frequent rejection episodes. In fact, rejection was a little less frequent in group 2 and only one patient required OKT3, whereas four patients in group 1 did so (Table 3). Rejection episodes occurred at similar time intervals in each group; low CyA levels did not appear to be a contributing factor (Table 4). Dosages of immunosuppressive therapy and CyA blood levels were very similar in each group, with no significant differences in the levels throughout the 1st year post-transplantation (Table 5).

Actuarial graft survival was also superior in group 2: 89% at 1 year compared to 65% at 1 year for group 1 (Fig 1). This, however, was not significant when tested by the log rank method ($X^2 = 2.27$; $P = 0.13$). The five grafts that never functioned had all sustained vascular thrombosis, histology confirming the presence of acute ischaemia and necrosis. Patient survival in both groups was 100%.

Discussion

In this study we have shown that with a triple therapy regimen, CyA administration can be delayed for 12 h post-transplantation and that this will secure an improvement in both immediate and long-term graft function. There seemed to be no disadvantages associated with this protocol and certainly rejection was not increased. We were surprised to note the relatively high rate of delayed function and rather poor outcome for the patients in group 1. A protocol of pre-operative CyA has been used by us for many years, and over this period the frequency of delayed function has been 35%. The higher rate in this study is not easily explained and may merely relate to the rather small number of patients enrolled. We would recommend, nonetheless, that when patients are commenced on a triple therapy, CyA administration should be delayed for 12 h to allow a diuresis to commence.

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