Improved patient and graft survival using cyclosporin A in cadaver renal transplantation

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SUMMARY

In two consecutive prospective randomised trials cyclosporin A has been compared with conventional immunosuppressive therapy (azathioprine and steroids) and with cyclosporin combined with steroids. The present report is a 4 year review and includes 165 patients.

Cyclosporin A alone had a significant advantage over conventional therapy at both 1 and 3 years ($p = 0.02$) for both patient and graft survival. No significant difference was seen when cyclosporin was combined with steroids. Nephrotoxicity was the most troublesome side-effect of cyclosporin A — but this resolved spontaneously on withdrawal of the drug.

INTRODUCTION

Since October 1980, 165 patients have been entered into two consecutive prospective randomised trials of the immunosuppressive drug cyclosporin A and have been followed up for a minimum of six months and a maximum of 4.5 years. In the first study cyclosporin A is compared with a conventional immunosuppressive régime of azathioprine and steroids. In the second, cyclosporin A alone is compared with cyclosporin A plus steroids. These studies have been conducted in a single centre with a large experience (600 patients) of conventional immunosuppressive therapy following cadaver renal transplantation.

PATIENTS AND METHODS

Only non-diabetic recipients of first and second cadaver renal grafts were considered. Every patient had previously received at least one blood transfusion; grafts were allocated on the basis of the least number of HLA-AB and DR mismatches. All patients received 500 mg methylprednisolone intravenously inra-operatively. Urine output was monitored hourly for the first six hours post-operatively and if it equalled or exceeded 50 ml/hr the recipient was entered into the trial by drawing a card to determine immunosuppressive therapy.

Group I Conventional therapy:
Azathioprine 3 mg/kg body weight
Soluble prednisolone 0.5 mg/kg body weight (to a maximum dose of 30 mg daily)

Group II Cyclosporin A alone:
Cyclosporin A was started as a continuous intravenous infusion 6 mg/kg body weight for 12 hr or until drugs could be accepted orally.

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Thereafter it was given in divided doses totalling 17 mg/kg/day in milk. The dose was reduced by 2 mg/kg at 2 weeks and 4 weeks, and then reduced monthly down to 5 mg/kg. In the event of toxic side-effects the dose was reduced by one-third. If toxicity continued or was intolerable the patients were switched to conventional therapy.

**Group III** Cyclosporin A plus steroids:

This group received cyclosporin A as above; in addition they were given low dose soluble prednisolone 0.25 mg/kg (to a maximum dose of 15 mg daily).

Acute rejection had to be distinguished from nephrotoxicity; this was most often accomplished by biopsy. Confirmed rejection was treated by daily injections of 1 g methylprednisolone for 3 days. It was a condition of the trial that only two rejection episodes should be treated in the cyclosporin A group and a maximum of 6 g steroid given. If graft function remained impaired or there was further deterioration the patients was switched to conventional therapy.

There were no serious imbalances of selection in any of the treatment groups. Age and sex were similarly distributed. HLA-AB and DR mismatches were close to 1.5 in the conventional group and 1.8 in the cyclosporin treated groups. All patients who lost their grafts and returned to dialysis were followed up for 1 year and included in the mortality data.

**RESULTS**

For ease of presentation and because the results were exactly the same the two cohorts of patients treated with cyclosporin alone have been combined.

Graft survival for the three treatment groups is shown in Table I. All patients who initially received cyclosporin are included in the graft survival analysis for the cyclosporin group, regardless of whether or not they were subsequently converted to conventional therapy (‘intention to treat’ principle). One year graft survival was 80.2% (65 of 81 grafts) in the cyclosporin alone group; this did not change significantly when steroids were added with survival at 78.6% (22 of 28 grafts). Both groups did significantly better than the conventional group where graft survival was 66% (37 of 56).

| Group                           | No. | 3 months | 1 year | 2 years | 3 years |
|--------------------------------|-----|----------|--------|---------|---------|
| Azathioprine and steroids       | 56  | 78%      | 65%    | 57%     | 57%     |
| Cyclosporin A alone             | 54  | 90%      | 80.2%  | 78.4%   | 78.4%   |
| Cyclosporin A alone             | 27  | 95.2%    | 78.6%  | 74.9%   | 74.9%   |
| Cyclosporin A and steroids      | 28  | 95.2%    | 78.6%  | 74.9%   | 74.9%   |

Cyclosporin A alone and cyclosporin A with steroids are significantly better than azathioprine and steroids at every stage (p = 0.02).

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Included in the cyclosporin alone group are 42 patients (51.8%) who were converted to conventional therapy (Table II) either because they required more than 6 g methylprednisolone for treatment of acute rejection (16 patients trial condition) or because of side-effects of cyclosporin (26 patients). One year graft survival in this sub-group is 76.2% (32 of 42 grafts): this is significantly better than for conventional treatment (p = .02). The incidence of conversion to conventional therapy was much lower (25% or 7 of 28), when steroids were combined with cyclosporin (Table III). This was because cyclosporin toxicity was reduced; conversion for rejection remained the same. Overall only one of 29 grafts was lost following conversion for toxicity whereas 13 out of 20 were lost when conversion was due to rejection.

**TABLE II**
Conversion from cyclosporin A to conventional therapy
(No. at risk = 81)

| Reason   | No. | Grafts lost |
|----------|-----|-------------|
| Toxicity | 26  | 1           |
| Rejection| 16  | 9 (56.25%)  |
|          | 42  (51.8%) | 10 (23.8%) |

**TABLE III**
Effect of concomitant steroid therapy on rate of conversion from cyclosporin A to conventional therapy

| Reason for conversion | Cyclosporin A alone (No. at risk 27) | Cyclosporin A + steroids (No. at risk 28) |
|-----------------------|--------------------------------------|-----------------------------------------|
|                       | No. | Grafts lost | No. | Grafts lost |
| Toxicity              | 11  | 0           | 4   | 1           |
| Rejection             | 2   | 1           | 3   | 3           |
|                       | 13  (48%) | 1 | 7 (25%) | 4 |

In the cyclosporin alone group there were 3 deaths (Table IV), only one of which was related to immunosuppression. There were two deaths in the cyclosporin plus steroids group, one of which was due to viraemia. The highest mortality was in the conventional therapy group (6 of 56). Four of these could be attributed to immunosuppression.

The commonest side-effects amongst the cyclosporin treated patients were hirsutism 44%, fine tremor 39%, gingival hypertrophy 28%, nephrotoxicity 25%, hyperaesthesia 11% and hyperkalaemia 9%. Most of these side-effects were minor and all were dose-related. They disappeared rapidly when cyclosporin was withdrawn or its dose reduced sharply. Nephrotoxicity was the commonest reason for conversion to conventional therapy. In patients on conventional therapy the commonest side-effects related to steroid therapy: cushingoid
TABLE IV
Causes of death

| Treatment group | Diagnosis                  | Days post-op | Graft status |
|-----------------|----------------------------|--------------|--------------|
| Cyclosporin A   | 1. myocardial infarction   | 350 days     | functioning  |
| alone           | 2. cerebral thrombosis     | 115 days     | functioning  |
|                 | 3. peritonitis (CAPD)      | 200 days     | lost         |
| Azathioprine    | 1. sepsis                  | 170 days     | lost         |
| + steroids      | 2. cerebral thrombosis     | 41 days      | functioning  |
|                 | 3. carcinoma pancreas      | 288 days     | functioning  |
|                 | 4. viraemia (CMV)          | 43 days      | lost         |
|                 | 5. viraemia (Herpes)       | 9 days       | lost         |
|                 | 6. sepsis                  | 130 days     | lost         |
| Cyclosporin A   | 1. viraemia                | 31 days      | lost         |
| + steroids      | 2. sclerosing peritonitis  | 252 days     | functioning  |
| (CAPD)          |                            |              |              |

appearance 54%, peptic ulceration 2% and diabetes 2%. These effects were also present when steroids were combined with cyclosporin. There was no difference in the frequency of bacterial, viral and fungal infections in the three groups but there was a difference in incidence of life-threatening infections. There were no life-threatening infections among the patients with cyclosporin alone whereas there were 8 in the conventional group resulting in 4 deaths and there were 3 amongst patients treated with cyclosporin and steroids resulting in one death.

DISCUSSION
These results confirm the view that renal allograft survival is greater in patients treated with cyclosporin alone as a first line immunosuppressive drug than in those treated with azathioprine and steroids. Our main interest in cyclosporin was its steroid-sparing potential; the significant improvement in graft survival without the side-effects of steroids was a bonus. The results we obtained for one year graft survival in patients treated with azathioprine and steroids accurately represent our previous experience with these drugs over the last 10 years. Improved graft survival (80.2%) with cyclosporin alone is similar to results obtained by the Cambridge group\(^1,2\) and by the European Multicentre Study.\(^3\)

Cyclosporin A differs greatly from all previously used immunosuppressive agents. The main problem in clinical use is distinguishing between nephrotoxicity and rejection. Most of the classical inflammatory features of acute rejection are absent. Serum creatinine is the only easily measurable determinant. Cyclosporin nephrotoxicity has been well documented\(^4,5\) and it is known to disappear on withdrawal of the drug. In this study many people were treated for rejection and then converted to conventional therapy as a condition of the trial, only to discover in retrospect that nephrotoxicity had been the problem. This resulted in an unacceptably high rate of conversion, 51.8% to conventional therapy. Sixteen patients (20.15%) were converted for rejection and to avoid the consequences

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of over-immunosuppression reported by the Cambridge group. Of these, 10 subsequently lost their grafts. Twenty-five patients (30.8%) were converted for toxicity without graft loss. These changes reflect inexperience in the use of cyclosporin and also the lack of a meaningful assay. There is now evidence that much lower doses of cyclosporin can be used in conjunction with careful whole blood monitoring of the drug. Under these conditions improved graft survival is maintained and toxicity minimised. Our approach was to try and exclude rejection by biopsy and then reduce the dose by one-third. If a satisfactory result was obtained the dose was further reduced until the side-effects disappeared (therapeutic titration).

Graft survival results in the sub-group of patients converted to conventional therapy was 76.2%; this was still significantly better than the conventional group, and it is of particular interest that only one graft was lost when conversion was because of toxicity.

Steroids were combined with cyclosporin to see if graft survival could be further improved and in particular to see if nephrotoxicity was reduced. Graft survival was not significantly different when cyclosporin was given with maintenance steroids (78.6%) but the rate of conversion for toxicity was significantly reduced, 14.28% compared with 40.7%. Conversion for rejection was the same in the two groups. This advantage for maintenance steroids has to be balanced against the increased rate of steroid side-effects for no improvement in graft survival.

In these studies we have limited entry to recipients with primary renal failure which excluded diabetic subjects and only included grafts that exhibited prompt diuresis. This was done in order to minimise the variables. Clearly the steroid-sparing aspect of cyclosporin therapy should have advantages in the treatment of diabetics. Very few exclusions were made on grounds of no primary diuresis. 74% of kidneys used in this study were machine-perfused and, contrary to the Canadian Multicentre Trial Report, this appears to have improved the rate of entry and in no way adversely affected the outcome. Cyclosporin A alone has now become our first choice immunosuppressive agent. We no longer convert for persistent rejection, preferring loss of the graft if necessary, and we are attempting to reduce toxicity by daily monitoring of whole blood trough levels of the drug.

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