Cadaveric Renal Transplantation With Cyclosporin-A and Steroids

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SINCE the introduction of Imuran and prednisone in 1961, and despite the addition of other adjuncts such as antithymocyte globulin (ATG) or thoracic duct drainage and the recognition of the importance of DR typing and blood transfusion, the major limitation to successful renal transplantation has been the lack of selective immunosuppression. Standard immunosuppression has yielded graft survival rates of 50%–65%, with a high price in infections and other morbidity due to the high steroid doses required. With the fortuitous discovery of the immunosuppressant activity of cyclosporin-A,[1] its testing in experimental animals,[2,3] and demonstration of its efficacy in human transplantation,[4–7] the possibility seems to exist of making a quantum leap in clinical transplantation. In March 1981, a randomized prospective trial comparing Imuran and prednisone with cyclosporin-A and prednisone in patients undergoing primary cadaveric renal transplantation was begun. This article reports the early results of that trial as well as the more recent experience utilizing cyclosporin-A in high-risk patients undergoing both primary and repeat cadaveric transplantation. These early results confirm the potent immunosuppressive effect of cyclosporin-A, the safety in conjunction with low doses of steroid, and the problem of nephrotoxicity.

RANDOMIZED STUDY

All patients accepted for primary cadaver transplant were eligible for study. Informed consent was obtained. All patients had received at least 3 U of type-specific whole blood prior to transplant. Upon completion of final crossmatch between donor lymphocytes and recipient serum, patients were randomized by computer-generated cards drawn in sequence to receive either Imuran and prednisone or cyclosporin-A and prednisone immunosuppression. The Imuran group received azathioprine, 5 mg/kg, for the first 3 days posttransplant, then tapered to a maintenance dose of 2.5 mg/kg/day over the next 2 weeks. Methylprednisolone (1 g) was given i.v. preoperatively. Prednisone was begun on the day after surgery at 2 mg/kg/day and tapered to a dose of 0.5 mg/kg/day over 3 weeks. Subsequently, the prednisone dose was tapered to 0.25 mg/kg/day by 1 year. The Cyclosporin-A-treated group received cyclosporin-A 17.5 mg/kg 4–6 hr preoperatively by mouth. The same dose was given daily thereafter in two divided doses. After 1–2 months, the dose was reduced to 12–14 mg/kg/day and subsequently to 3–10 mg/kg/day depending on the clinical course. Methylprednisolone (1 g) was given i.v. preoperatively. Prednisone was given on the first postoperative day (200 mg) and reduced by 40-mg decrements over 5 days to 20 mg/day. This was subsequently reduced to 10–15 mg/day, depending on the clinical course. Figure 1 shows the comparison of steroid doses in the early postoperative period. All patients in the cyclosporin-A group continued to receive full doses of cyclosporin-A whether or not there was immediate graft function. Rejection was diagnosed on clinical grounds. Treatment in each group consisted of recycling prednisone and in most cases, 450 rad graft radiation in 3 divided doses on alternative days.

Twenty-one patients were randomized to the cyclosporin-A group and 20 to the Imuran

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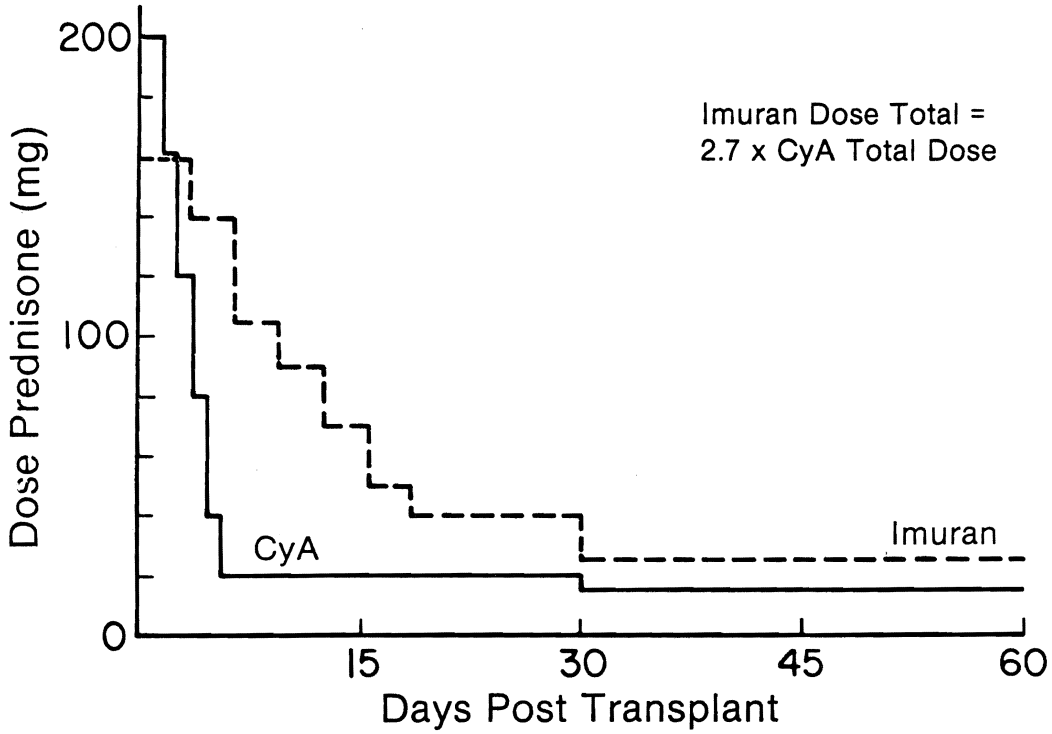

Fig. 1. Comparison steroid doses.

group. Table 1 lists the characteristics of each group. One-year graft survival for the cyclosporin-A group is 91%. One-year graft survival for the Imuran group is 56%. (Fig. 2). Two patients lost their kidneys in the cyclosporin-A group—one due to accelerated rejection due to receiving an ABO incompatible kidney, a violation of the protocol, the other due to cessation of immunosuppression due to a bowel perforation. No other kidneys were lost. Nine patients lost kidneys in the Imuran group—all to rejection. There were no deaths in either group (Fig. 3).

Table 1. Randomized Imuran Versus Cyclosporin Trial: First Cadaveric Transplantation

	Imuran	Cyclosporin-A
Number of patients	20	21
Age range	20–56	25–61
Mean age	42.8	41.7
Mean A and B antigen match	1.2	1.0
Mean A and B antigen mismatch	2.6	2.7
Number of diabetics	4	4

Nephrotoxicity was a common sequela to the use of cyclosporin-A, as were tremor, hair growth, and gum hyperplasia, though these latter were seldom troublesome. Most adjustments in cyclosporin-A dose were made on clinical evidence of toxicity and carried out on an out-patient basis. The 1-year creatinine, cyclosporin-A, and steroid doses of the patients in the randomized trial are listed in Table 2.

Thirty-eight total patients were transplanted with cyclosporin-A and low dose prednisone in 1981 and 31 with the Imuran protocol. Graft survival overall was 92% and 55%, respectively. A comparison of the infection rates between the two groups shows a rate twice as high for the Imuran-treated patients, while most infections encountered in the cyclosporin-A group were less serious. (Table 3).

Because of the demonstrated superiority of the cyclosporin-A and low steroid regimen, randomization was stopped, and the cyclosporin-A/steroid schedule was used for all

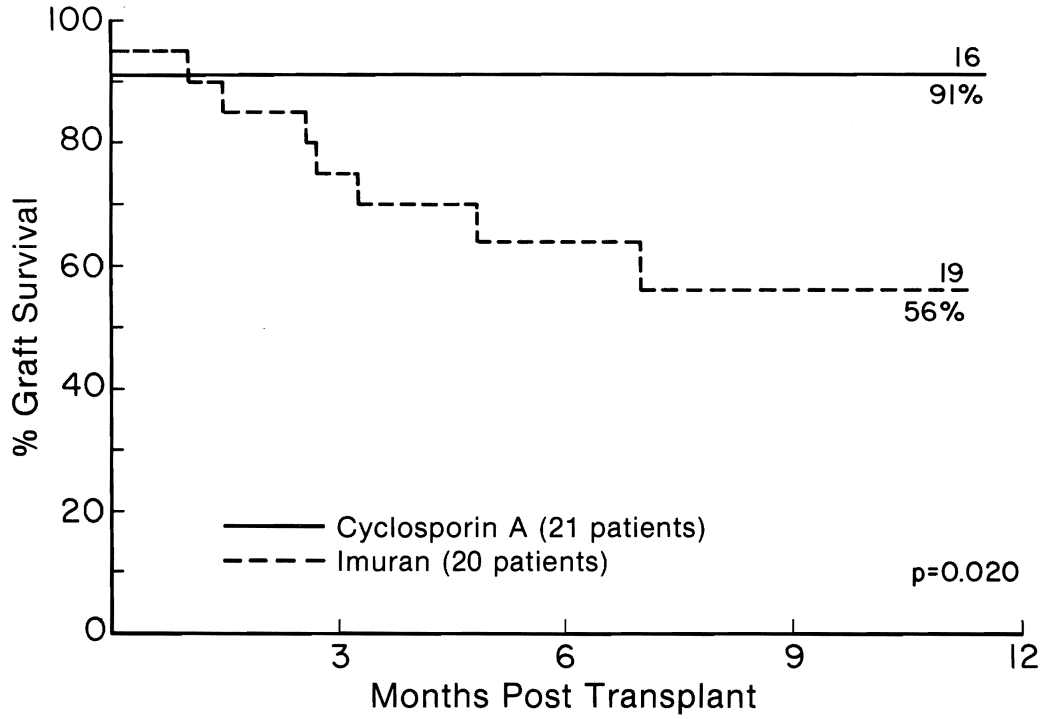

Fig. 2. Primary cadaveric renal transplant prospective randomized trial—1981.

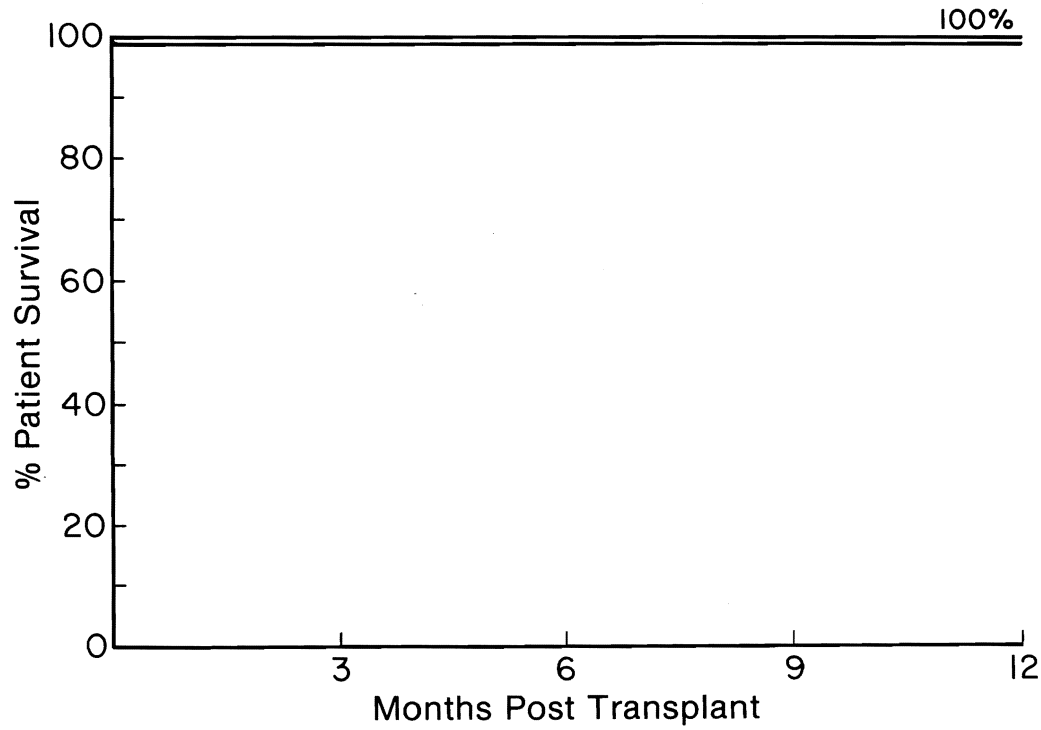

Fig. 3. Patient survival Cyclosporin A Imuran randomized trial.

Table 2. Mean Posttransplant Levels

	3 Months	1 Year
Cyclosporin-A	10 mg/kg/day	6 mg/kg/day
Prednisone	14 mg/day	12 mg/day
Creatinine	1.94 mg/dl	1.98 mg/dl

patients undergoing cadaveric transplantation over the past 16 months, including a large number of high-risk patients. Included in these 133 patients were 65 patients over 40 years of age, 22 with diabetes mellitus, 18 with antibodies to greater than 70% of random lymphocytes tested, and 40 undergoing second, third, or fourth transplant of whom 27 lost their previous graft in less than 1 year (Table 4). Overall 1-year graft survival is 83% (Fig. 4). Overall patient survival is 95%. Seven deaths have occurred—5 from acute myocardial infarction (3 in diabetics over age 45), 1 from sepsis secondary to bowel perforation, and 1 from complications from sickle-cell disease. Eleven patients have lost grafts secondary to rejection. Four of these were primary transplants; 7 were repeat transplant patients. One of these patients was noncompliant, having a perfectly functioning kidney until stopping immunosuppression. The characteristics of the remaining 10 patients show 7 with percent reactive antibodies (PRA) greater than 70% and 6 complete HLA mismatches (Table 5).

Two malignancies have been seen in these patients. One was a bowel lymphoma that was resected; the other was a Kaposi's sarcoma that resolved spontaneously on reduced cyclosporin-A dose. Both patients are alive with functioning kidneys.

Table 4. Cyclosporin-A Patient Population (133)

Primary nondiabetic	71
Repeat transplant	40
Diabetic	22
Mean HLA match	1.0
No. over 40 years of age	66
No. with PRA 70%	18
No. with positive crossmatch to non-concurrent serum	5

DISCUSSION

This study confirms the potential usefulness of cyclosporin-A and low dose steroid to enable a high rate of graft survival with a low cost in morbidity or mortality. The results are similar to those reported by others testing the drug using a similar protocol.[8] The most efficacious dose schedule has yet to be worked out, though the basic tenets of management that have proven successful are: beginning the drug preoperatively and continuing regardless of early diuresis or not, rapid tapering of steroid early in postoperative period, tapering cyclosporin-A over a longer period depending on clinical manifestations of toxicity. The rational for this approach has been discussed elsewhere.[9] The early concerns about high incidence of lymphoma have not been evident so far.[10] Two patients in this series have developed tumors, neither of which have proven lethal.

Infection rate is significantly lower in cyclosporin-A-treated patients. Other salutary effects due to decreased steroid requirements such as fewer cataracts, improved sense of well being, decreased Cushinoid appearance, and fewer bone problems are apparent

Table 3. Infections in Cadaver Kidney Transplants 1981

Imuran (32)		Cyclosporin-A (66)	
Pneumocystis pneumonia	3	Pneumocystis pneumonia	3
Pneumococcal pneumonia	1	CMV pneumonia	1
Staph pneumonia	1	Generalized CMV	1
Osteomyelitis	4	Febrile UTI	2
Perinephric abcess	1	PID	1
		Sinusitis	1
		Epididymitis	1
Total	10 (31%)	Total	10 (15%)
3 Grafts lost		0 Grafts lost	

Table 5. Characteristics of Patients With Rejection (11)

No. 0 antigen match	6
No. PRA >70%	7
No. noncompliant	1
No. active CMV	1
No. repeat transplant	6
No. positive crossmatch	1

to those treating these patients, but not yet quantitated.

Aside from the problem of resolving precise dosage schedules and balancing nephrotoxicity, two other areas of concern exist. One is the long-term safety and efficacy, which will be answered in time. The other is its use in high-responder patients, be this measured by level of preformed antibodies, time to failure of previous transplants, or simply retrospectively by the emergence of accelerated rejection. Although in this series of five patients transplanted against a positive crossmatch to both T and B cells in nonconcurrent sera, only one lost their graft. Eighteen patients had preformed antibodies against greater than 70% of tested lymphocytes in both peak and concurrent sera; 7 of these patients lost kidneys to rejection, a graft survival much less than the remainder of the group. Since this is the type of patient filling more and more transplant lists, it remains a significant problem if the 90% graft survival that is obtainable in other patients with cyclosporin-A and steroid is to be obtained in this high-responder group.

SUMMARY

Cyclosporin A and steroid was compared to Imuran and prednisone in a prospective, randomized study of patients undergoing primary cadaver renal transplantation. Graft survival was superior in the cyclosporin-A-treated group, with 1-year kidney function of 92% and less infections. No kidneys were lost to rejection in this group. Further experience with a variety of high-risk patients have reinforced this early experience, showing few kidneys lost to rejection and low incidence of infectious complications using cyclosporin-A and low dose steroid combination.

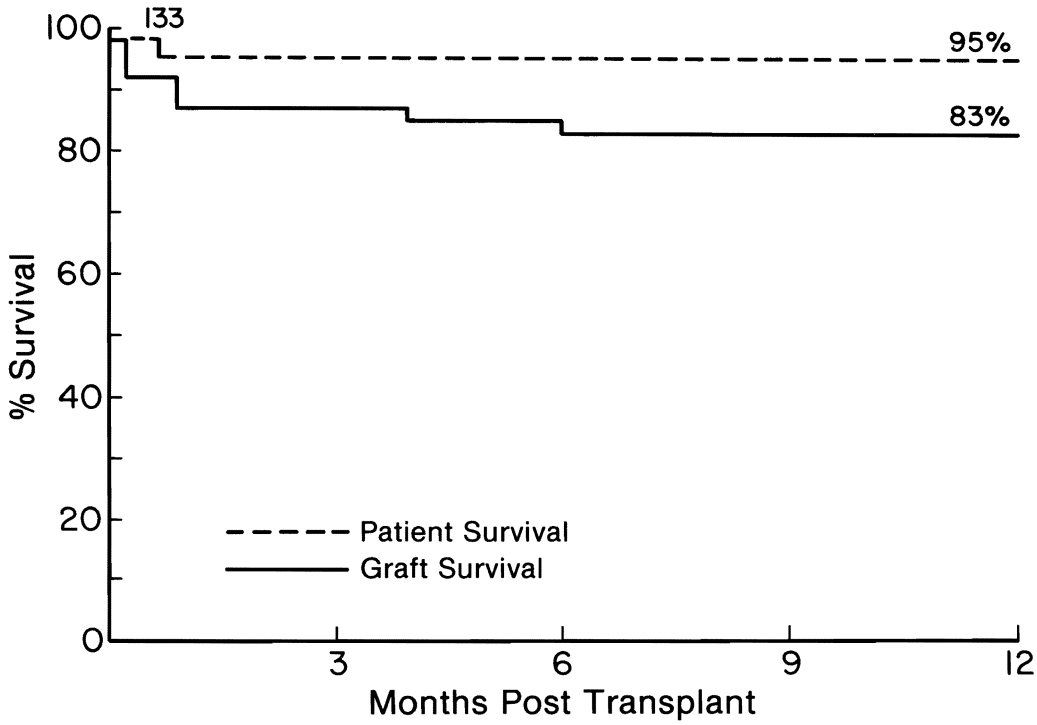

Fig. 4. Patient and graft survival Cyclosporin A 1981–1982.

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