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Cyclosporine-Steroid Combination Therapy in 84 Cadaveric Renal Transplants

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● **Sixty-three primary and 21 retransplant cadaver kidney allografts were placed in 77 patients over a one-year period with three- to six-month follow-up. Eight primary grafts (12.7%) and six retransplants (28.6%) were lost to rejection. Patient mortality was 3.9%. There were no grafts lost and no deaths due to opportunistic infections. Renal function at 6 months after transplantation was similar in all primary transplant recipients regardless of risk factors, including advanced age, diabetes, or the need for postoperative dialysis.**

INDEX WORDS: Cyclosporine; kidney transplant.

RESULTS previously reported from this center for cadaver renal transplants performed during 1981 demonstrated the superiority of combination cyclosporine-prednisone therapy over conventional immunosuppression with azathioprine and steroids.[1-3] Encouraged by these results, the resources of the general surgery division concentrated on expansion of the liver transplant program with similar success during 1982 and 1983.[4]

In November 1983, we resumed a program in cadaveric renal transplantation on the general surgery service at this center. We report here the results of the first 84 consecutive renal transplants performed using cyclosporine-steroid therapy between November 15, 1983 and November 15, 1984 with three- to six-month follow-up.

MATERIALS AND METHODS

Case Material

Primary cadaveric renal transplants were performed in 63 patients with a mean age of 45.6 ± 11.4 (SD) years (range 9 to 68 years). Twenty-one retransplantations were performed, including seven patients from the primary series who lost their first grafts within six months. There were 13 patients in the series with type I insulin-dependent diabetes mellitus. Additional demographic features of the patients are given in Tables 1 and 2.

Patients were selected for transplantation based only on the results of the preoperative screen for preformed antidonor cytotoxic antibodies. Patient selection was not based on HLA—A, HLA-B, or DR typing or historical panel reactive antibody (PRA). None of the patients received deliberate pretransplant transfusions.

Operation

Renal allografts from heart beating cadavers were harvested using the in-situ flush technique recently described for multiple organ procurements.[5] All grafts were separated immediately after harvesting and stored in iced Collins' solution. Grafts were implanted within 18 to 30 hours after harvesting using a conventional method.[6]

Immunosuppression

The rationale for combined cyclosporine-prednisone therapy has been previously described.[1-3] Whenever possible, patients received a 17.5 mg/kg oral loading dose of CsA 4 to 6 hours prior to surgery. No further CsA was given until after surgery. If oral loading was not possible, 2 mg/kg intravenous CsA was administered over one hour intraoperatively after revascularization of the graft was completed.

Renal recipients usually resumed oral intake within 12 to 24 hours after surgery and could be maintained on oral CsA 17.5 mg/kg per day in two divided doses. If needed, this was supplemented or replaced by intravenous CsA, 2 mg/kg given two or three times per day. Whole blood CsA trough levels were monitored daily using radioimmune assay technique.

Just prior to revascularization of the allograft, all patients received one gram of intravenous methylprednisolone. On the day after operation, a five-day burst of methylprednisolone or prednisone was begun starting at 200 mg per day, with daily reductions of 40 mg, until a maintenance level of 20 mg per day was reached. In high-risk patients, such as those with a previous history of acute allograft rejection or a high current PRA (> 30%), maintenance therapy was held at 30 mg per day. In children, the five-day cycle was begun at 100 mg per day and tapered to 20 mg per day.

Adjustments in the immunosuppressive regimen are often required during convalescence.[1] If a graft which functioned promptly after surgery deteriorated, rejection was suspected. One gram of intravenous methylprednisolone was administered followed by a recycle of the steroid taper. CsA dosage was modified as needed to achieve adequate blood levels, but be-

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Table 1. Patient Demographics

	Number	Mean Age ± SD	Age Range: Younger than 14 Years	Age Range: 50 Years or Older	Diabetics	Male	Female
Primary grafts	63	45.6 ± 1.6	1	28	12	45	18
Retransplants	21	34.9 ± 2.5	1	3	1	16	5

cause of the acute nephrotoxic potential of CsA, there was usually little room for upward adjustment of this agent.

If a graft was oliguric or anuric following surgery, the standard regimen was administered. If no improvement in function occurred within 10 to 14 days, treatment for rejection as described previously was begun. Downward adjustment of CsA dosage was frequently made during periods of severe oliguria or anuria.

RESULTS

Patient Survival

There were two perioperative deaths and one late death. A 47-year-old diabetic with documented right coronary artery disease sustained a fatal intraoperative myocardial infarction. A 61-year-old nondiabetic with a previous anteroposterior resection for colorectal carcinoma died five weeks after operation of gastrointestinal hemorrhage and sepsis.

The one late death in this series occurred from a myocardial infarction one month after allograft nephrectomy for chronic rejection at seven months after transplantation. The patient, a 32-year-old diabetic, also had a mild myocardial infarction several weeks after his transplant operation.

Operative mortality in this series was two patients out of 77 (2.6%) with an overall series mortality of three out of 77 (3.9%).

Table 2. Basis of Renal Disease in 77 Patients

Etiology	No. of Patients
Glomerulonephritis	15
Diabetes mellitus	13
Hypertensive nephrosclerosis	11
Polycystic kidney disease	8
Lupus nephritis	3
Pyelonephritis	3
Interstitial nephritis	3
Gouty nephropathy	2
Alport's syndrome	2
Obstructive uropathy	1
Focal sclerosis	1
Scleroderma	1
Wegener's granulomatosis	1
Analgesic nephropathy	1
Unknown	12

Graft Survival

Graft survival is summarized in Table 3. Eight primary grafts have been lost to rejection (12.7%). Two grafts were lost to acute rejection (3.2%). Six grafts were lost to chronic rejection (9.5%), including one graft lost when a patient stopped taking his CsA. Forty eight grafts (76.2%) are functioning three to six months after transplant.

Seven patients who lost their primary grafts were retransplanted and four of these patients have functioning grafts. Fourteen additional patients received retransplants, eight of which were successful. Thus, 12 of 21 (57.1%) retransplanted patients have functioning grafts three months (4 patients) to six months (8 patients) after surgery.

Renal Function

Mean serum BUN, creatinine, CsA level, and CsA dose in patients with a functioning primary cadaver allograft are summarized in Table 4. There was no significant change in renal function as measured by BUN and creatinine in the first six months. At hospital discharge, mean serum creatinine was 2.3 ± 0.8 (SD) mg%. Six months after transplantation, mean serum creatinine was 2.1 ± 0.9 (SD) mg%.

Twenty five of the 48 successful primary transplants required a mean of 13.9 ± 7.8 (SD) days of dialysis after surgery (Table 5). Average urine output in the first 48 hours after transplantation was 2,852 ± 2,872 (SD) mL for all 48 successful primary grafts. In patients requiring dialysis in the first week after surgery, the average first 48-hour urine output was 1,205 ± 1,220, SD mL compared to an average output of 4,583 ± 2,000 (SD)

Table 3. Graft Survival

	Primary Grafts (N = 63)	Retransplants (N = 21)
Grafts functioning at three months	11	5
Grafts functioning at six months	37	7
Total grafts functioning	48	12
Percent graft survival	76.2%	57.1%

Table 4. Renal Function After Cadaveric Renal Transplantation

	Primary Grafts	Range (N = 48)	Retransplants	Range (N = 12)
Hospital days	28.5 ± 10.7	10–53	31.8 ± 10.2	14–45
At hospital discharge				
BUN (mg%)	44.8 ± 20.6	13–148	49.7 ± 13.1	29–73
Creatinine (mg%)	2.3 ± 0.8	0.9–4.3	2.7 ± 1.7	1.0–6.9
CsA level (ng/mL)	920 ± 320	329–1587	732 ± 239	405–1207
Three months after transplant				
BUN (mg%)	40.7 ± 13.3	21–86	46.2 ± 16.9	23–84
Creatinine (mg%)	2.1 ± 0.7	1.0–4.3	2.1 ± 0.9	1.4–4.6
CsA level (ng/mL)	843 ± 358	359–2273	776 ± 401	130–1489
CsA dose (mg/kg/d)	8.6 ± 4.5	3.0–22.0	7.2 ± 3.3	4.0–15.0
Six months after transplant	N = 37		N = 7	
BUN (mg%)	39.6 ± 11.9	20–64	40.4 ± 10.0	29–56
Creatinine (mg%)	2.1 ± 0.9	1.0–6.0	2.0 ± 0.4	1.6–2.9
CsA level (ng/mL)	737 ± 212	310–1241	563 ± 209	241–889
CsA dose (mg/kg/d)	6.9 ± 3.3	3.0–20.0	5.1 ± 1.5	3.0–8.0

Mean ± SD.

mL in patients not requiring dialysis. Mean serum creatinine remained unchanged in patients with prompt graft function and was significantly better than mean serum creatinine at hospital discharge ($P < 0.02$), and at three months after transplantation ($P < 0.05$) in patients whose grafts had delayed function. However, at six months after transplantation, there was no significant difference in mean serum creatinine based on early graft function (Table 5).

Age Groups

There was only one pediatric allograft recipient in this series. A 9-year-old boy with Alport's syndrome received a primary cadaver graft and required retransplantation for chronic rejection after five months. His second graft is functioning well six months after transplantation.

Table 5. Effect of the Need for Postoperative Dialysis on Graft Function

	Immediate Function (N = 23)	Required Dialysis (N = 25)
First 48-hour urine output (mL)	4583 ± 2000	1205 ± 1220
Hospital days	25.6 ± 12.0	31.2 ± 8.7
At hospital discharge		
BUN (mg%)	39.3 ± 14.8	49.9 ± 24.0
Creatinine (mg%)	2.0 ± 0.7	2.5 ± 0.9
Three months after transplant		
BUN (mg%)	38.7 ± 13.9	42.5 ± 12.8
Creatinine (mg%)	1.8 ± 0.5	2.3 ± 0.8
Six months after transplant	N = 20	N = 17
BUN (mg%)	39.5 ± 13.3	39.6 ± 10.4
Creatinine (mg%)	2.0 ± 1.1	2.2 ± 0.7

Mean ± SD.

Twenty eight patients aged 50 years or older (range, 50 to 68 years) received cadaver allografts. Twenty three of these patients have functioning allografts (82.1%). Renal function for allografts in these older patients was not significantly different than the level of function achieved in younger patients (Table 6).

CsA

At discharge from the hospital, mean trough CsA blood levels in the 48 patients with functioning primary allografts was 920 ± 320 (SD) ng/mL (Table 4). Three months after transplantation, mean CsA trough level was 843 ± 358 (SD) ng/mL and at 6 months, 737 ± 212 (SD) ng/mL. Blood levels in the retransplanted patients were not significantly different (Table 4). Three months after transplantation, primary recipients were taking an average of 8.6 ± 4.5 (SD) mg/kg per day of CsA. At six months after transplantation, the

Table 6. Effect of Patient Age on Graft Function

	Younger than 50 Years (N = 25)	50 Years and Older (N = 23)
Hospital days	28.7 ± 10.2	28.3 ± 11.3
At hospital discharge		
BUN (mg%)	45.8 ± 25.8	43.7 ± 13.4
Creatinine (mg%)	2.3 ± 0.8	2.3 ± 0.8
Three months after transplant		
BUN (mg%)	40.7 ± 13.4	40.6 ± 13.5
Creatinine (mg%)	2.1 ± 0.7	2.1 ± 0.7
Six months after transplant	N = 21	N = 16
BUN (mg%)	40.6 ± 11.7	38.3 ± 12.4
Creatinine (mg%)	2.0 ± 0.5	2.3 ± 1.3

average CsA dose was 6.9 ± 3.3 (SD) mg/kg per day.

Hypertension, tremors, gingival hyperplasia, and hypertrichosis were seen to some degree in all patients. Hypertension was the most troublesome side effect and over 75% of the patients required multiple drug therapy to control it.

Significant hepatic dysfunction occurred in three patients. One lost his graft as a complication of recurrent wound hemorrhages and another lost his graft to renal vein thrombosis. The third patient improved with reduction in CsA dose and continues to have good graft function after six months.

There have been no lymphoproliferative lesions in the patients in this series so far. No patients have been converted from CsA-prednisone therapy to conventional therapy with azathioprine and steroids. Four allografts with steroid resistant rejection were rescued with a course of OKT-3 monoclonal antibody (Ortho Pharmaceutical Corp, Raritan, N.J.).

Hospitalization

The mean duration of hospital stay for the successful primary transplant patients was 28.5 ± 10.7 (SD) days (Table 4). Primary recipients with prompt graft function required 25.6 ± 12.0 SD days. Those patients who required early postoperative dialysis were hospitalized 31.2 ± 8.7 (SD) days (Table 5). Patients aged 50 years and older were discharged after a mean stay of 28.3 ± 11.3 (SD) hospital days and patients younger than 50, after 28.7 ± 10.2 (SD) hospital days (Table 6). Diabetics were hospitalized 31.6 ± 9.4 (SD) days versus 27.8 ± 10.9 (SD) days for nondiabetics (Table 7). There are no significant differences among these figures for hospital stay for any of these selected patient groups.

Table 7. Effect of Diabetes on Graft Function

	Diabetics	Non-diabetics
Number transplanted	12	51
Number of functioning grafts	9 (75.0%)	39 (76.5%)
Hospital days	31.6 ± 9.4	27.8 ± 10.9
At hospital discharge		
BUN (mg%)	64.3 ± 32.6	40.3 ± 13.8
Creatinine (mg%)	2.8 ± 0.9	2.2 ± 0.8
Three months after transplant		
BUN (mg%)	49.0 ± 16.4	38.8 ± 11.9
Creatinine (mg%)	2.5 ± 1.0	2.0 ± 0.6
Six months after transplant	N = 6	N = 31
BUN (mg%)	49.2 ± 7.0	37.7 ± 11.8
Creatinine (mg%)	2.7 ± 0.6	2.0 ± 0.9

Mean ± SD.

Thirty three readmissions to the hospital in 19 patients are summarized in Table 8. CsA toxicity necessitated readmission on nine occasions (27.3%). Infections required eight admissions (24.2%). Three patients developed late ureteral obstruction. One patient required intraperitoneal drainage of a lymphocele. Two patients required uretero-ureterostomy for obstruction of the graft ureteral implant. Two of these three grafts are still functioning and one was lost to chronic rejection.

Infections

There were 20 opportunistic infections in this series. Nine cases of herpes simplex or herpes zoster were treated with systemic therapy. Four cases of cytomegalovirus infection with positive buffy coat, urine, or throat wash cultures were documented. Seven cases of pneumocystis carinii pneumonia required hospitalization, reduction in immunosuppressive therapy, and antibiotics. All patients recovered and no grafts were lost.

Diabetes

Thirteen of the 77 patients in this series were transplanted for diabetic nephropathy. Nine of 12 primary graft recipients have a functioning kidney three to six months after transplantation. Two grafts were lost to chronic rejection within six months.

Renal function in diabetic and nondiabetic primary recipients is summarized in Table 7. Mean serum creatinine in the diabetic recipients at hospital discharge was 2.8 ± 0.9 (SD) mg% and at 3 months 2.5 ± 1.0 (SD) mg%. These values are significantly higher than discharge creatinine (2.2 ± 0.8 [SD] mg%, $P < 0.05$) and 3 month creatinine (2.0 ± 0.6 [SD] mg%, $P < 0.05$) in the nondiabetic patients. However, at 6 months creatinine in diabetic recipients (2.7 ± 0.6 [SD]

Table 8. Indications for 33 Hospital Readmissions

Indication	No. of Patients
CsA toxicity	9
Infection	8
Allograft rejection	7
Uncontrolled diabetes	3
Ureteral obstruction	3
Miscellaneous medical problems	2
Hypertension (without CsA toxicity)	1

mg%) was not significantly different than creatinine in non-diabetics (2.0 ± 0.9 [SD] mg%).

Two diabetics developed serious forefoot infections requiring a major amputation within 6 months after transplantation. Both patients continue to have functioning grafts. There were no deep wound infections or perigraft abscesses in any patients.

Gastrointestinal Complications

Two patients developed severe postoperative colonic distension requiring a surgical decompression. One patient was treated with a colostomy and bowel continuity was restored within three weeks. The kidney was lost to renal vein thrombosis. A second patient suffered microperforations of the cecum requiring a limited right colon resection with exteriorization of the colon and ileum. Bowel continuity was restored eight weeks later. The patient's graft is functioning well. One death from gastrointestinal hemorrhage and sepsis was discussed previously.

DISCUSSION

Forty eight of 63 primary cadaver renal allografts are functioning three to six months after transplantation. Four of seven patients whose primary grafts failed were successfully retransplanted within a short interval. Even with a high technical loss rate (7.9%) in the first six months of this series, 52 of 63 (82.7%) primary patients ultimately left the hospital with a functioning graft.

Twelve of 21 patients (57.1%) given retransplants have functioning kidneys three to six months after operation. Three of the six grafts lost to rejection were in patients with a panel reactive antibody in excess of 40%. The transplant waiting list in Pittsburgh, as in many other centers, contains a large percentage of patients with a high PRA.

These results were achieved with an overall patient mortality of less than 4% and modest morbidity. Diabetics are at higher risk of death from cardiac complications than nondiabetics. We continue to use liberal criteria for pretransplant cardiac catheterization and coronary revascularization in diabetic candidates for kidney transplantation.

A major advantage of CsA is the ability to use the drug effectively with lower doses of steroids than was possible with azathioprine without an increased risk of graft loss. Only six of 83 grafts (7.2%) have been lost to chronic rejection despite maintenance doses of 10 mg prednisone per day in most patients within 3 months of transplantation. Herpes viruses, cytomegalovirus infections, and pneumocystis carinii pneumonia remain a threat, but all cases in this series were managed by reduced immunosuppression and appropriate antibiotic therapy without graft loss or mortality.

Renal function remained stable in nearly all patient groups during the three- to six-month follow-up period. Although the level of renal function early after transplantation was better in nondiabetic than in diabetic patients, the number of diabetics in the series was small (13 patients) and the differences were not detectable six months after surgery. Neither postoperative renal dysfunction requiring dialysis nor advanced age had an impact on functional results after transplantation.

The high incidence of posttransplant dysfunction requiring dialysis (52%) reported here reflects the very strict inclusion of all patients requiring any dialysis in the first week after transplantation. In our experience, prompt renal function relates most directly to expeditious transfer of the graft from donor to recipient. Most of the kidneys transplanted in this series were implanted 18 to 30 hours after in-situ perfusion. Ten kidneys implanted with less than 18 hours cold ischemia time all functioned promptly.

CsA nephrotoxicity can produce oliguria or anuria and can prolong postoperative dysfunction. We have been willing to accept the short-term consequence, of acute CsA nephrotoxicity to minimize graft loss from acute rejection. However, we try to avoid intravenous use of CsA in the perioperative period whenever possible and rely instead on a single oral loading dose 4 to 6 hours prior to surgery. During convalescence, we will reduce CsA dosage in the face of oliguria or anuria.

The CsA dosages and blood levels reported here reflect aggressive use of the drug which has enabled us to achieve low rates of graft loss from rejection. However, two recent developments have led us to reconsider our current protocols for use of CsA and steroids. Chronic interstitial fibrosis of the kidney has been reported 12 to 18 months after cardiac transplantation[7] and renal transplantation[8] and may relate to high levels of CsA given in the first six months. Secondly, monoclonal antilymphocyte antibody has been available to us in recent

months and was used to rescue four grafts in this series with steroid-resistant rejection. We now have a new generation of triple drug therapy with CsA, low-dose prednisone, and monoclonal antibody to replace the older triple drug regimen of azathioprine, high-dose prednisone, and ALG.

During most of this series, it was our policy to aim for 12-hour CsA trough levels (whole blood RIA) between 800 and 1200 ng/mL during the first few months after transplantation, which required 10 to 15 mg/kg CsA per day. Within six months of transplantation, patients were tapered to 5 to 8 mg/kg per day with 12 hour trough levels in the 650 to 750 ng/mL range. Mean serum creatinine level in this series at six months is around 2 mg% and may reflect a persistent level of nephrotoxicity.

Presently, we are accepting postoperative 12 hour trough levels between 600 to 750 ng/mL and permit levels to fall to 400 to 600 within several months. Monoclonal antibody offers an escape route for patients for whom these reduced doses of CsA are inadequate to prevent acute rejection. It is possible that further downward reductions in CsA will be required to reduce the risk of chronic renal damage.

A few patients have been encountered who are exquisitely sensitive to CsA and require drastic reduction in dosage. Nine of the 77 patients in this series are being maintained on a single daily oral dose sufficient to maintain a 24-hour trough blood level of 150 ng/mL. There is little margin in these patients between nephrotoxicity and adequate immunosuppression.

Lymphoproliferative disorders have been reported in association with CsA-prednisone therapy.[9] Reduction or cessation of immunosuppressive therapy is the treatment of choice in this situation. We have not encountered any of these lesions in the present series as yet.

The side effects of CsA—including hypertension, hypertrichosis, gingival hyperplasia, tremors, seizures, paresthesias, and flushing—are common and often troublesome. However, they are often easily managed by modest reductions in dosage.

We continue to select patients for transplantation with CsA-prednisone therapy based on the results of the screen for specific antidonor cytotoxic antibody without regard for the results of HLA-A, B, or DR typing and without a program of deliberate pretransplant transfusion. The excellent results that can be obtained with current immunosuppressive therapy do not, in our opinion, justify either a more restrictive selection process based on typing or the risk of sensitization imposed by deliberate transfusion.

Current DRG criteria for renal transplantation permit 24 days of hospitalization with reimbursement of a little more than $17,000. We found that our mean hospital stay was 28 days and it is estimated that hospital charges in our center are approximately $600 per day. Therefore, in this center we are incurring an average cost of about $16,800 per transplant, which is in agreement with current DRG based financing.

SUMMARY

Sixty-three primary and 21 retransplant cadaver kidney allografts were placed in 77 patients over a one-year period with three- to six-month follow-up. Eight primary grafts (12.7%) and six retransplants (28.6%) were lost to rejection. Patient mortality was 3.9%. Renal function at six months after transplantation was similar in all primary transplant recipients regardless of risk factors including advanced age, diabetes, or the need for postoperative dialysis. There were no grafts lost and no deaths due to viral or pneumocystis carinii infections. Average hospital stay was 28 days at a cost of approximately $16,800 which is in good agreement with current DRG based reimbursement. The availability of monoclonal antibody for graft rescue should permit use of lower doses of CsA to reduce the risk of chronic nephrotoxicity.

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