# CADAVERIC RENAL TRANSPLANTATION UNDER CYCLOSPORINE-STEROID THERAPY

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THE FIRST CLINICAL TRIALS of renal transplantation with cyclosporine therapy were reported four years ago by Calne and associates (1, 2) who recommended from their experience that the drug should be used alone. In our own pilot trials (3, 4), the alternative was developed of combining cyclosporine with steroid therapy which was administered in large doses on the day of the operation and rapidly reduced to relatively low maintenance levels. Although the results were encouraging, they were not conclusive since there were no patients for comparison who were treated during the same period with conventional immunosuppression. We report herein upon a second trial of cadaveric renal transplantation, in which the results using cyclosporine-steroid therapy for primary cadaveric transplantation could be compared with those in patients treated contemporaneously with azathioprine and prednisone. Experience was also acquired with patients who underwent cadaveric retransplantation.

## METHODS

Ninety-seven cadaveric renal homografts which were obtained from brain dead donors were transplanted into 96 recipients in 1981. The 96 recipients were placed into three general study groups (Table I) which were defined by two factors: the immunosuppressive therapy and a distinction between primary transplantation versus retransplantation. The three groups were comparable for recipient age, incidence of diabetes mellitus and prior transfusion history. Donor-recipient matching at the A and B loci was poorest in those in group 1 who had primary grafts under cyclosporine and steroids (Table I). Dr typing data were incomplete and are not presented.

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Among the 26 patients who underwent retransplantation (group 3), the sera of ten (38.5 per cent) had warm anti-T lymphocyte cytotoxic antibodies which reacted against one-half or more of a lymphocyte panel contributed by 48 healthy donors. This condition was present only seven times (18 per cent) for primary transplantation under cyclosporine-steroids (group 1) and twice (6 per cent) for primary transplantation under azathioprine-prednisone (group 2).

In nine of 96 recipients, T-warm antibodies were present which reacted against more than 90 per cent of the panel (Table I). For five transplantations—one in group 1, none in group 2 and four in group 3—there were T-warm antibodies in the recipient sera that had been collected as recently as three weeks earlier which completely killed the lymphocytes of the actual donor, although cross matches were negative using sera drawn on the day of the operation. In most centers, such findings are construed as a positive cross match and preclude transplantation.

Patients in groups 1 and 3 were given 17 milligrams per kilogram per day of cyclosporine on the day of the operation as well as a five day burst of prednisone which was begun at 200 milligrams in adults and reduced by daily decrements of 40 milligrams in uncomplicated instances to a daily maintenance level of 20 milligrams. The details of therapy, the variability of convalescence, the indications for deviation from the original treatment regimen and the need to distinguish between rejection and cyclosporine nephrotoxicity in planning drug dose changes early or late after transplantation have been described elsewhere (5).

Azathioprine-prednisone therapy for primary cadaveric transplantations for those in group 2 was with a formula that has been used in many centers, including this institution, for several years. Azathioprine was given in a dose of 5 milligrams per kilogram on the day of the operation and weaned to a plateau dose of 2 milligrams per

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TABLE I.—FEATURES OF 97 CONSECUTIVE CADAVERIC TRANSPLANTATIONS

| Group | Total patients | Total grafts | Age mean ± S.D. years | Age <18 | Age >55 | Patients with type I diabetes | ≥3 previous transfusions | A, B Antigen matches mean ± S.D. | >50 per cent T-warm antibodies in recipient sera | >90 per cent antibodies |
|---|---|---|---|---|---|---|---|---|---|---|
| 1, Cyclosporine-steroids (primary) | 38 | 38 | 36.5±16.8 | 3 | 7 | 6 | 26 | 0.79±0.9 | 7 | 2 |
| 2, Azathioprine-steroids (primary) | 32 | 32 | 39.4±14.6 | 4 | 7 | 7 | 28 | 1.53±1.1 | 2 | 1 |
| 3, Cyclosporine-steroids (retransplantation) | 26 | 27 | 31.3±14.5 | 3 | 3 | 1 | 25 | 1.46±1.3 | 11 | 6 |

kilogram per day within four days. This dosage was maintained unless bone marrow depression mandated a further reduction. Prednisone was started at 2 milligrams per kilogram per day with decrements of 0.25 milligrams per kilogram every five days until a daily maintenance dose of 0.4 milligrams per kilogram per day was reached after 30 days in uncomplicated instances. Rejection was treated with augmented steroid dosages.

The principal comparisons were between the primary cadaveric groups 1 and 2 in which 21 and 20 patients, respectively, were part of a seven month randomized trial which was terminated prematurely because of the wide divergence of results. The complete patient material in groups 1 and 2 included 17 and 12 additional patients, respectively. Several of these extra patients were treated in 1981 just before or after the randomized trial. Others specifically requested that one or the other type of immunosuppression be used after an informed consent briefing. A few could not participate in the randomized trail because they were minors. The results for the full groups 1 and 2 and the strictly randomized subgroups were analyzed separately.

Because of the historically poor results with cadaveric retransplantation under conventional immunosuppression as reported by Husberg and Starzl (6) and Asher and co-workers (7), all patients in group 3 received cyclosporine-steroid therapy. The results for those in group 3 were compared with those after cadaveric retransplantation during the preceding three years at this institution. Within group 3, comparisons were made between patients with and without widely reacting T-warm antibodies.

## RESULTS

### *Patient Survival*

The one year mortality for the entire study was 2.1 per cent (two of 96). Both deaths were after primary transplantation. A 55 year old man with known coronary artery disease died of a myocardial infarction three weeks after primary transplantation under cyclosporine-steroid therapy; he had good renal function. A 43 year old woman in group 2 had rejection of the kidney within four months under azathioprine-steroid therapy and died of a gastrointestinal hemorrhage three months later after returning to chronic dialysis. An additional patient in group 1 died of a mid-gut infarction 17 months after transplantation. This 51 year old recipient had had a myocardial infarction before transplantation and two more infarctions afterward. Renal function under cyclosporine and steroids was satisfactory until the time of death.

The one year mortality after retransplantation was zero (group 3). However, a 41 year old man with a well functioning graft died of a ruptured abdominal aortic aneurysm 18 and one-half months postoperatively. After 15 to 27 months, 92 of the 96 patients entered into the study were alive (95.8 per cent).

### *Kidney Survival*

*Group 1, (primary graft, cyclosporine-steroids).* Thirty-four of 38 kidneys (89.5 per cent) survived for one year and all but one that was lost by late death are still functioning after 15 to 24 months (Fig. 1a). Only one of these patients has been switched to azathioprine. Nineteen of the 21 kidneys (90.5 per cent) in the strictly randomized subgroup survived for one year and beyond; all 19 grafts still function (Fig. 1b).

*Group 2 (primary graft, azathioprine-steroids).* Sixteen of 32 grafts (50 per cent) survived for one year (Fig. 1a) but another kidney was lost to rejection after 13 months. Fifteen of the transplants (47 per cent) are still functioning after 16 to 26 months. Eleven of 20 grafts (55 per cent) in the strictly randomized subgroup functioned for at least one year, but one of these kidneys was rejected at 13 months (Fig. 1b). The results for those in the complete group 2 or its randomized subgroup were significantly poorer than for the comparable complete or partial group 1 (Fig. 1).

*Group 3 (retransplantation, cyclosporine-steroids).* The one year graft survival rate was 21 of 27 (77.8 per cent). Further grafts were lost to

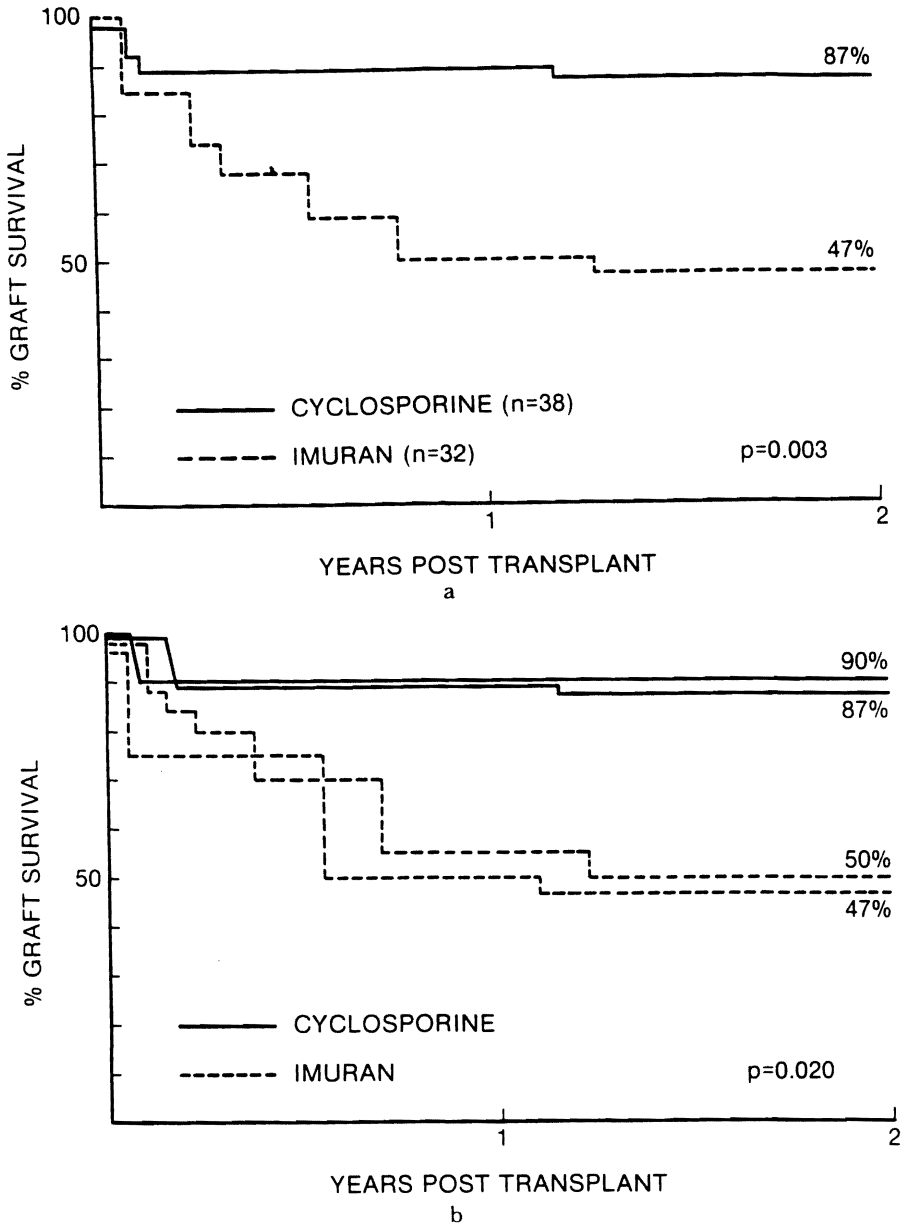


FIG. 1. a, The survival rate of kidneys after all primary cadaveric transplantations, in 1981, is shown. Follow-up studies were for at least 15 months. b, Results in randomized subset of 1981 experience, compared with the total results. Note that both the experimental (cyclosporine-steriods, 21 patients) and conventional (azathioprine-steroids, 20 patients) randomized limbs were 3 per cent higher than in the total groups.

chronic rejection after 13 and 15 months, and as the result of death after 18 and one-half months. The graft survival rate after 15 to 25 months is 18 of 27 (66.7 per cent). None of the patients still bearing a graft has been changed to azathioprine. The results were twice as good as were achieved during the preçeding three years with azathioprine-steroid therapy (Fig. 2).

The one year survival rate was 14 of 16 kidneys (87.5 per cent) in group 3 which were transplanted to recipients in whom sera had T-warm antibodies against less than 50 per cent of the lymphocyte panel (Table II). The presence of more widely reacting antibodies had an adverse effect upon the results (Table II). Of the four patients in group 3 in whom stored preoperative sera contained antigraft antibodies, three had graft function of at least one year.

*Cause of Graft Losses*

In group 1, three kidneys were lost to rejection and one from death (Table III). One of the rejec-

TABLE II.—EFFECT OF T-WARM ANTIBODIES ON OUTCOME AFTER RETRANSPLANTATION UNDER CYCLOSPORINE-STERIODS

| | *No. of grafts* | *One year survival rate* |
|---|---|---|
| Antibodies < 50 per cent panel | 16 | 14 (87.5) |
| Antibodies > 50 per cent and < 90 per cent panel | 5 | 4 (80) |
| Antibodies > 90 per cent panel | 6 | 3 (50) |
| Total | 27 | 21 (77.8) |

Numbers in parentheses are percentages.

tions was of the hyperacute variety after a blood typing error resulted in transplanting an A kidney to an O recipient; another rejection occurred after an intestinal perforation necessitated discontinuance of immunosuppression. Rejection under immunosuppression with azathioprine and steroids caused the loss of 16 primary grafts in group 2 (Table III). In spite of cyclosporine-steroid therapy, graft losses from acute or chronic rejection occurred five times after retransplantations in group 3 (Table II).

*Renal Function*

The serum creatinine concentrations of patients still bearing functioning grafts are not demonstrably different in the three groups (Table IV).

*Final Cyclosporine Dosages*

At the end of the first year, the patients in group 1 were receiving an average daily dose of 5.2±1.8 (S. D.) milligrams per kilogram and the recipients in group 3 received 5.8±2.0 (S. D.) milligrams per kilogram. The maintenance dosages in both groups reflected the weaning that had been carried out, often in response to nephrotoxicity.

*Steroid Consumption in Groups 1 and 2*

The culling process caused by the heavy loss of kidneys under conventional therapy made comparison of a steroid dosage decreasingly valid with time. However, the cumulative doses of prednisone during the first two months, in patients who had immunosuppression continued this long, was 2.7 times greater in the recipients treated with azathioprine than in those who were given cyclosporine (8).

TABLE III.—CAUSE OF GRAFT LOSS IN FIRST YEAR

| | *Group 1* | *Group 2* | *Group 3* |
|---|---|---|---|
| Rejection | 3* | 16 | 5 |
| Technical complication | 0 | 0 | 1 |
| Death | 1 | 0 | 0 |

*1 ABO mismatch; 1 after cessation of immunosuppression because of bowel perforation, and 1 despite standard drug administration.

*De Novo Malignant Disease*

In recipient groups 2 and 3, new tumors were not seen. Two patients in group 1 who received primary cadaveric homografts under cyclosporine-steroid therapy had a neoplasm develop. One of the tumors was a polyclonal B-cell lymphoma in a 20 year old male who had evidence of an Epstein-Barr virus infection. The lymphoma caused perforation of the ileum which was treated with an intestinal resection and a major reduction in cyclosporine and steroid dosages (5). The patient is well one and one-half years later with no evidence of persistent tumor and with normal renal function.

The other neoplasm was a multifocal Kaposi sarcoma, mostly of the upper extremities but also involving the legs. The lesions appeared at the same time as increases occurred in cytomegalovirus antibody titers. After the results of the biopsy confirmed the diagnosis, the patient was treated with a reduction of the cyclosporine dose from 10 to 1.2 milligrams per kilogram per day as reported by Little and co-workers (9). Over the ensuing 13 months, the lesions disappeared completely while renal homograft function has remained excellent. There were no examples of new epithelial malignant growths in any of the groups.

## DISCUSSION

Because of the low (2.1 per cent) one year patient mortality, assessment of the effectiveness of immunosuppression was almost free of the analytical artifact sometimes introduced by patient deaths despite satisfactory graft function. The survival rate of 89.5 per cent of the primary cadaveric grafts for one year and beyond using cyclosporine-steroid therapy was possible in the absence of good tissue matches, without uniform recipient preparation with transfusions and with a mix of patients at low, intermediate and high risk. The one year primary cadaveric graft survival rate of 50 per cent in the control group using azathioprine-steroid therapy was the same as that in large multicenter compilations as reported by Opelz (10) and McDonald and co-workers (11), although this was slightly lower than obtained at our center during the previous two years.

The direct comparison of cyclosporine-steroid immunosuppression with the conventional double drug combination of azathioprine and steroids has special practical importance because the latter therapy is, by far, the most widely used in the world today. Even when cyclosporine has been given alone, reserving steroids for the specific indication of rejection, the results of European (12)

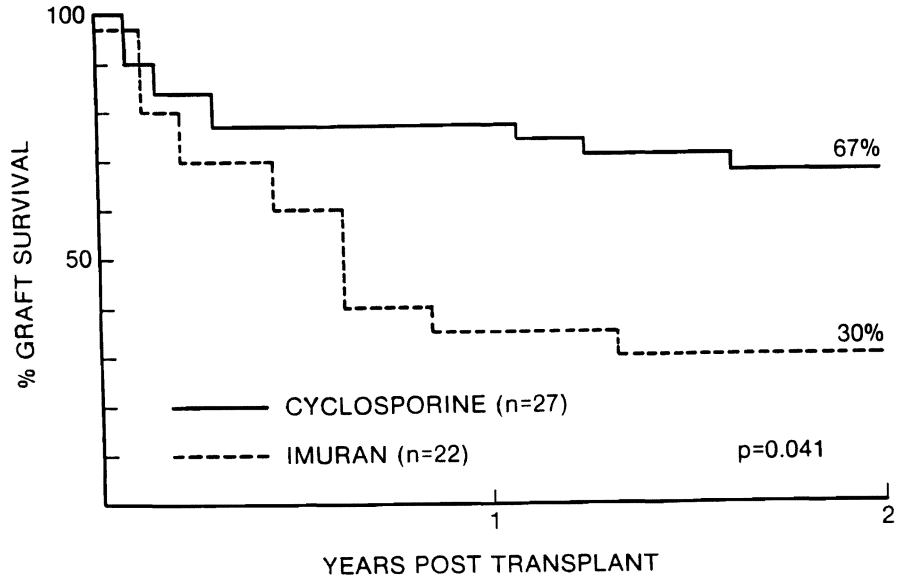


FIG. 2. The graft survival rate after cadaveric retransplantation under cyclosporine-steroids compared with historical control groups. All follow-up studies are for at least 15 months.

and Canadian (13) trials have shown an advantage over azathioprine-steroid therapy.

In another randomized trial at a single institution, Ferguson and co-workers (14) compared cyclosporine-steroid therapy to triple drug therapy with azathioprine, prednisone and antilymphoblast globulin (ALG). The graft survival in both groups was so high that differences were undetectable by this criterion. However, patients in the cyclosporine-steroid limb had fewer infections, fewer rejections, reduced steroid needs, shorter hospital stays and a smaller number of readmissions. The triple drug regimen for patients in control groups has long been thought to provide improved immunosuppression as reported by Starzl and co-workers (15) and Najarian and associates (16), but difficulties with the expense, standardization, inconvenience, limited duration (because of sensitization) and the risk of ALG have restricted its use to a minority of centers.

Nephrotoxicity, hepatotoxicity, hypertension, tremors, gum hyperplasia, hirsutism and flushing are side-effects of cyclosporine. All are relieved by dosage reduction, which may be guided by serial measurements of blood or plasma cyclosporine levels as shown by Kahan and associates (17). However, management with clinical criteria is relatively easy. The most important practical problems in renal recipients are the differentiation of rejection from nephrotoxicity as reported by Calne and co-workers (2, 18), and Starzl and associates (3, 4, 5).

In the first clinical trials with cyclosporine as reported by Calne and co-workers (2), almost 10 per cent of the patients had lymphomas develop. In a subsequent experience reported by Bird (19), the incidence of lymphomas under cyclosporine or cyclosporine-steroid therapy has been little different than with conventional immunosuppression, and almost all have been associated with Epstein-Barr virus infections. Much remains to be learned of the behavior of these lesions which, in the world experience with cyclosporine, have not been responsible for the death of any renal recipient as noted by Penn (20). Our approach to therapy has been to reduce drastically the dosages of both cyclosporine and steroids and to excise the tumor if possible (4, 5). In patients treated with azathiopine, prednisone and ALG, the disappearance of lymphoma-like neoplasms after discontinuance of immunosuppression has been described (21). The same principle probably applies to the therapy of other neoplasms that have been associated with viruses. For example, a multicentric Kaposi's sarcoma in one of our patients treated with cyclosporine disappeared after major dosage reductions. There has been a singular ab-

TABLE IV.—SERUM CREATININE LEVELS (MGM PER CENT) (AFTER 15 TO 27 MONTHS)

| | *Group 1* | *Group 2* | *Group 3* |
|---|---|---|---|
| No. functioning | 33/38 | 15/32 | 18/27 |
| No. creatinine < 3.0 mgm. per cent | 32 | 15 | 18 |
| No. creatinine ≥ 3.0 mgm. per cent | 1 | 0 | 0 |
| Mean ± S.D. mgm. per cent all patients | 1.97±0.50 | 1.61±0.60 | 1.92±0.54 |

sence in patients treated with cyclosporine of epithelial neoplasms which account for 75 per cent of the malignant diseases under conventional immunosuppression as reported in a study by Penn (22).

The results of late follow-up study of patients treated with cyclosporine in the pilot trials of 1978 to 1980 have shown that the drug can be administered chronically as reported by Calne and associates (18) and Starzl and co-workers (23). Unusual late complications have not been seen, providing that the daily cyclosporine dosages are slowly reduced with the passage of time.

The impact of cyclosporine-steroid therapy upon transplantation policies and End Stage Renal Disease programs should be major. The ability to carry out cadaveric transplantation safely, effectively and with low maintenance steroid doses may limit or make obsolete the use of living related donors. More patients considered at high risk because of age, diabetes mellitus or other factors could be considered for transplantation candidacy. Public education to increase support of cadaveric donor procurement will be a corollary. With the realization that retransplantation can be successful, the temptation for over immunosuppression will be lessened and the mortality should decline. Tissue typing, which has never been a precise instrument for donor-recipient matching in cadaveric transplantation as reported by Opelz and co-workers (10) and McDonald and associates (11), will become even less important. Conversely, detection of presensitization states, including those signaled by cytotoxic antibodies, will be more important. Deliberate blood transfusions, in preparation for transplantation to improve graft survival, will become less prevalent since the penalty of sensitizing a significant number of potential recipients and rendering them nontransplantable will not be necessary. Finally, the interface between dialysis and transplantation will be changed. With more patients seeking the greater rehabilitation that is offered by transplantation, the mounting costs of the End Stage Renal Disease program should be reduced.

SUMMARY

Ninety-seven cadaveric renal transplants were performed upon 96 patients during 1981. The one year patient mortality was 2.1 per cent. Seventy of the recipients were undergoing transplantation for the first time. Of these patients, 38 were treated with cyclosporine and steroids with a one year graft survival rate of 89.5 per cent. The other 32 primary recipients were treated with azathioprine and steroids with a one year graft survival rate of 50 per cent. The difference between the cyclosporine-steroid versus conventional therapy groups was significant. Cyclosporine and steroids also were used to treat 26 patients who underwent retransplantation with 27 cadaveric grafts. The one year graft survival time was 77.8 per cent; most of the graft losses were in presensitized patients. The results with retransplantation were twice as good as in historical control groups.

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