The Colorado-Pittsburgh Cadaveric Renal Transplantation Study with Cyclosporine

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OUR EXPERIENCE with cyclosporine for cadaveric renal transplantation began in late 1979. An article by Calne et al.[1] had just been published that gave critics of our trial a lot of ammunition. Although the path-finding report by Calne and his associates contained the good news that rejection of some cadaveric kidneys had been avoided with no drug other than cyclosporine, the bad news was that there had been a high patient mortality in these Cambridge trials, that none of the kidneys was providing normal function, and that nearly 10% of the recipients had developed lymphomas.[1]

MATERIALS AND METHODS

In spite of these warning signs, a large-scale clinical trial of cadaveric renal transplantation was mounted; this is now 3½ years old (Table 1). Sixty-six patients were treated at the University of Colorado in a non-randomized trial between December 1979 and September 1980. This was a learning period in which it was realized that cyclosporine should be used with steroids for optimum efficiency.[2] However the exact formula for the prednisone interaction with cyclosporine had not yet been worked out. In addition, the dose manipulation of cyclosporine that was frequently necessitated by the nephrotoxicity of this drug had not yet been clarified. These subtleties of management were described later[3,4] and were applied in the Pittsburgh series.

RESULTS

Phase I (1979–1980)

The results in the Colorado trials were surprisingly good in spite of a learning curve effect (Table 2). Almost 80% of the primary cadaveric grafts were still functioning at the end of 1 year, as well as 60% of the cadaveric kidneys used for retransplantation.

The 1-year results have held up well. Now, with a median follow-up of about 3 years, 68.4% of the primary grafts and half of the grafts used for retransplantation are still providing satisfactory function. The 3-year patient mortality in the trial has been 21.2%.

Phase II (1981)

The most important part of the study encompassed the calendar year 1981, during which, at the University of Pittsburgh, 65 cadaveric kidneys were transplanted to 64 patients (Table 3). Thirty-eight of the patients were primary graft recipients under cyclosporine-steroid therapy. The other 26 were undergoing retransplantation after one

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Table 1. Three Phases of Cyclosporine-Steroid Cadaveric Kidney Trials

Phase	Year(s)	Location	Primary Transplantations	Retransplantations
I	12/1979–9/1980	Colorado	57	10 (9 patients)
II	1981	Pittsburgh	38*	27 (26 patients)
III	1982	Pittsburgh	96	22

*Part of randomized trial against azathioprine-steroid therapy, which was used for 32 patients.

or more kidneys had been rejected or lost for other reasons at some time in the past. At the same time, 32 patients who were part of a randomized trial had primary cadaveric transplantation under azathioprine and prednisone.

By this time a firm idea had evolved about the expectations after cadaveric transplantation under cyclosporine-steroid therapy and the appropriate therapeutic response under varying postoperative conditions.[4] The standard postoperative recipe in adults receiving 17.5 mg/kg/day cyclosporine was a 5-day burst of prednisone, beginning with 200 mg/day, and with daily decrements of 40 mg until, after 6 days, a maintenance dose of 20 mg/day had been reached. An untroubled convalescence without rejection was called a Class I course. Patients who developed what was thought to be a rejection in spite of this treatment were given a second 5-day steroid burst, often with a bolus or two of steroids in addition. Secondary deterioration of renal function characterized a Class II recovery. In such patients, chronic high-dose steroid therapy was not permitted. An upper limit of 30 mg/day prednisone as a maintenance dose was placed on adults. If recovery did not follow with this conservative approach, it was assumed that cyclosporine nephrotoxicity was responsible, and the dose of this drug was reduced.

A third kind of postoperative evolution, termed Class III, was in patients who either had no postoperative urine output at all or whose initial urine excretion was minimal.[4] Such recipients were treated with the same 5-day burst of steroids as patients with a perfectly benign recovery, and no other adjustments were made for about 2 weeks. Then, manipulation of either the cyclosporine or steroid doses was considered.

Only about one-third of the patients had a Class I recovery. The majority had some secondary deterioration of function after reasonable initial performance by the graft and were said to have passed through a Class II convalescence. A few patients had complete anuria from the outset (Class III). The incidence of sustained good graft function was much higher in the patients undergoing primary transplantation than in those who were receiving retransplants.[4] In the latter immunologically high-risk recipients, there was a high incidence of widely reacting preformed antibodies.

Primary cadaveric recipients. By the end of the first postoperative year, two of the patients in the randomized trial (2.9%) had died, one each from the control and study groups. The 1-year survival of the cadaveric grafts under cyclosporine-steroid therapy was 89.5%, and under conventional immunosuppression it was 50%. This divergence in results

Table 2. Colorado Cyclosporine Trial (1979–1980)

Months	Survival (66 patients)	57 First Grafts	10 Retransplantations (9 patients)
0	66	57	10
6	58 (87.9%)	48 (84.2%)	6 (60%)
12	57 (86.4%)	45 (79.0%)	6 (60%)
18	57 (86.4%)	44 (77.2%)	6 (60%)
24	56 (84.8%)	43 (75.4%)	6 (60%)
32–42	52 (78.8%)	39 (68.4%)	5 (50%)

Table 3. Primary Cadaveric Transplantation, Pittsburgh Cyclosporine Trial (1981)

Months	Survival of Patients*	Graft Survival (Cyclosporine + Steroids)	Graft Survival (Azathioprine + Steroids
0	70	38	32
6	69 (98.6%)	34 (89.5%)	22 (68.8%)
12	68 (97.1%)	34 (89.5%)	16 (50%)
17–27	67 (95.7%)	33 (86.8%)	15 (47%)

*Two deaths in cyclosporine group from: myocardial infarction (3 weeks) and mesenteric infarction (17 months); one death in azathioprine group from gastrointestinal hemorrhage (7 months).

continued through a 1½-year period up to the present time, now with follow-ups of 17 to 27 months. A detailed analysis of the results has been published.[5]

The trial was brought to an end in December 1981. Toward the end of the trial, there was a genuine revolt among the patient population as well as among the personnel on the transplantation ward who realized the disadvantaged position in which the control patients being treated with azathioprine and prednisone were placed.

Cadaveric retransplantation. Meanwhile, in 1981, 27 cadaveric retransplantations were carried out in 26 patients. The large number of retransplantations was compiled because the staff and patients both came to realize that patients undergoing retransplantation were not being randomized and thus could count on being treated with cyclosporine. In this group (Table 4), the 1-year graft survival was 78%; now, with a median follow-up of 2 years, 67% of these grafts are still functioning. The results were more than twice as good as in a group of historical controls compiled over the preceding 3 years. The 1-year mortality in this difficult group of patients was zero, although a patient died 18½ months after transplantation of a ruptured abdominal aneurysm.

Table 4. Cadaveric Graft Survival After Retransplantation in 1981 (Cyclosporine Series)

Months	27 Retransplant in 26 Patients (Cyclosporine + Steroids)	22 Retransplants in 22 Patients (Azathioprine + Steroids)*
3	23 (85.2%)	15 (68.2%)
6	21 (77.8%)	13 (59.1%)
12	21 (77.8%)	8 (36.4%)
18	19 (70.4%)	7 (31.8%)
20–30	18 (66.7%)†	6 (27.3%)

*Historical controls.

†Of the three late graft losses, two were from chronic rejection after 12 and 13 months; the third was from death (ruptured aneurysm) after 18½ months. The death was the only one in the series.

Table 5. Cadaveric Cases in 1982 (Cyclosporine + Steroids)*

	No.	Deaths	Graft Function
Primary transplantation	96	10	77
Retransplantation	22	1	20

*Follow-ups 4½–16½ months.

Phase III (1982)

The results obtained in 1982 have been generally confirmatory of the earlier ones. Ninety-six primary cadaveric transplants were carried out in 1982; the graft survival after 5 to 16½ months is 78% (Table 5). The lower graft survival during this most recent year was due mainly to an almost 10% patient mortality, which for the most part was caused by myocardial infarctions and other complications of vascular disease. A loosening of the criteria of case selection was thought to have been responsible for the increased mortality. In contrast, 22 patients underwent retransplantation in 1982, with a present graft survival greater than 90% and with a 5% patient mortality (Table 5).

DISCUSSION

The way in which cyclosporine-steroid therapy will influence practices in renal transplantation is still speculative, but the new horizons opened thereby will be broad. Our own use of the drug now extends 3½ years, and beyond that there are a significant number of patients being followed by Calne et al. of England.[6] The possibility of treating patients for years with cyclosporine has been thoroughly demonstrated, although the ultimate maintenance doses of the drug reached in order to avoid nephrotoxicity have sometimes been surprisingly small.

The specter of lymphoma production with cyclosporine has been all but replaced with a comfortable understanding that most of the lesions grouped under this frightening classification are not true lymphomas as Rosenthal and others describe. The term *pseudo lymphoma* used by Iwatsuki et al. for such lymphoproliferative lesions may be an appropriate one.[7]

The good results obtained both in Denver and in Pittsburgh were without the kind of systematic recipient transfusion that has become so popular among nephrologists and without the kind of good tissue matching that at one time was envisioned as an important condition for successful cadaveric transplantation. The ways in which all of the observations made over the last several years could alter the so-called strategy of transplantation has been speculated upon elsewhere.[5] Because of the outstanding results obtained with cadaveric transplantation, the use of living donors has lost much of its attractiveness. The importance of tissue matching at the A, B, and D loci will be reduced. Since cyclosporine cannot prevent hyperacute rejection, the importance of accurately identifying preformed antidonor T-warm antibodies will be increased. As a corollary, it will become increasingly important to avoid sensitization of potential kidney recipients by deliberate transfusion. Because it has been so much easier to treat diabetics with the low steroid doses that are needed with cyclosporine, these patients have become more attractive candidates for cadaveric organs. Other patients of marginal candidacy will be more freely admitted to transplant waiting lists. The fact that the organ supply will become critical is quite obvious.

SUMMARY

The immunosuppression provided with cyclosporine and steroids has greatly increased the effectiveness of cadaveric kidney transplantation both in patients receiving their first kidneys and in those undergoing retransplantation.

REFERENCES

1. Calne RY, Rolles K, White DJG, et al: Lancet 2:1033, 1979

2. Starzl TE, Weil R III, Iwatsuki S, et al: Surg Gynecol Obstet 151:17, 1980

3. Starzl TE, Klintmalm GBG, Iwatsuki S, et al: Surg Gynecol Obstet 153:486, 1981

4. Starzl TE, Hakala TR, Rosenthal JT, et al: Surg Gynecol Obstet 154:819, 1982

5. Rosenthal JT, Hakala TR, Iwatsuki S, et al: Surg Gynecol Obstet 157:309, 1983

6. Calne RY, White DJG, Evans DB, et al: Br Med J 282:934, 1981

7. Iwatsuki S, Geis WP, Molnar Z, et al: J Surg Res 24:428, 1978

#542