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Kidney Transplantation Under FK 506 Immunosuppression

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WE RECENTLY reported our initial experience with FK 506 in 36 patients undergoing renal transplantation.[1] This series was characterized by a high average complexity, and included 10 patients who also were liver recipients either concomitantly or at an earlier time. Additionally, 2 of the 10 also were given a heart or pancreas.

We report here a follow-up of the 26 patients from that original experience who were pure kidney recipients, plus 39 more treated through June 3, 1990. The first pure renal recipient underwent her third cadaveric transplantation on April 14, 1989. She was highly sensitized (panel reactive antibody [PRA] 93%) and rejected the graft. The next effort, also a retransplantation, was made on September 13, 1989. This was successful. Consequently, the follow-up to be reported of surviving grafts is 2.5 to 11 months.

METHODS

The 65 patients were given a total of 66 grafts, all cadaveric except for 2 (father to daughter, sister to sister). Of the transplantations, 43 (65.2%) were primary. The other 23 (34.8%) were transplanted in patients who were receiving their second to fourth grafts, one secondary recipient being a failure from the primary series (Table 1). The mean recipient age was 39.9 ± 13.5 (SD) years, with 10 patients over the age of 55. Diabetes mellitus was the cause of renal failure in 19 of 65 (29.2%) recipients and glomerulonephritis was the cause in 13 (20%) patients. Several patients undergoing retransplantation often had the diagnosis of chronic rejection and/or cyclosporine (CyA) toxicity (Table 2).

Good HLA matches were uncommon. In 49 of 66 (74.2%) transplantations, only 0 to 2 of the 6 possible antigens were matched; 12 (18.2%) were performed with 3 antigen matches and 5 (7.6%) with 4. The mismatches reflected a generally similar histoincompatible pattern. With the mismatch assessment there were only 3 (4.5%), 1 (1.5%), and 8 (12.1%) examples of 0, 1, and 2 antigen mismatches, respectively.

Thirty of 65 (46.1%) patients were considered to be presensitized in that their dithiothreitol (DTT)-treated[2] current or stored sera contained antibodies against 11% to 98% of the 62 donors who contributed to the PRA screening tray; the PRA was >40% in 19.7%. In 6 (9.1%) of the patients, transplantation was performed across a weakly or unequivocally positive cytotoxic crossmatch using current or stored sera or both.

The mean cold ischemia time for the 64 cadaveric kidneys was 35.9 ± 9.8 hours. Forty-four (66.7%) of the organs were recovered elsewhere and sent to Pittsburgh. Pediatric en bloc kidneys from donors <3 years of age were used in 16 cases (24.2%). The oldest cadaveric kidney was from a 65-year-old donor. The mean donor age was 33.2 ± 16.4 years for the 50 kidneys which were not en bloc.

FK 506 and corticosteroids were used in all patients. The initial dose of 0.075 or 0.15 mg/kg FK 506 was usually started IV in the recovery room 2 hours after transplantation and given over 2 to 4 hours. In a few sensitized patients, FK 506 was begun intraoperatively. Further IV doses of 0.075 mg/kg were given every 12 hours until the patient could tolerate oral FK 506, which was begun at a dose of 0.15 mg/kg twice per day. In recent cases (not included here) IV FK 506 has been given as a continuous infusion of 0.10 or 0.15 mg/kg over 24 hours. Trough plasma FK 506 levels were measured using the method of Tamura et al.[3]

The first 25 patients received a 1000 mg bolus of IV methyl-

Table 1. Case Material

	Cadaveric	Living-Related	Total
Recipients	63	2	65
Grafts	64	2	66*
1st	42	1	43 (65.2%)
2nd	17	0	17 (25.8%)
3rd	4	1	5 (7.6%)
4th	1	0	1 (1.5%)

Note. Mean recipient age was 39.9 ± 13.5 years, including the only pediatric recipient who was 10 years old.

*One patient had a first and second cadaveric allograft during this time period (April 14, 1989 to June 3, 1990).

Table 2. Causes of Renal Failure

	Number (%)
Diabetes mellitus	19 (29.2)
Glomerulonephritis	13 (20.0)
Hypertension	7 (10.8)
Chronic rejection/ CyA damage	5 (7.7)
Polycystic kidney disease	5 (7.7)
Systemic lupus erythematosis	4 (6.2)
Focal segmental glomerulosclerosis	3 (4.6)
Chronic rejection	2 (3.1)
Hemolytic-uremic syndrome	1 (1.5)
IgA nephropathy	1 (1.5)
Sickle cell disease	1 (1.5)
Renal cell carcinoma	1 (1.5)
Medullary cystic disease	1 (1.5)
Congenital hypoplasia	1 (1.5)
Interstitial nephritis	1 (1.5)
Total	65

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prednisolone during the operation, followed by an attenuating prednisone burst which decreased from 200 mg to 20 mg/d over 6 days. The subsequent 40 patients were given 20 mg/d of prednisone from the outset. When possible, the steroid dose was tapered over the first several weeks and stopped. Supplementary steroids or OKT3 were given if rejection was suspected clinically or diagnosed with biopsy.

RESULTS

Graft Function and Survival

Forty-one of the 66 (62.1%) kidneys functioned immediately, while 25 (37.9%) had some form of delayed graft function, presumably from acute tubular necrosis (ATN). All but two of the ATN group required dialysis for at least 1 week after transplantation, with the longest delay being over 1 month before recovery. Three more grafts have good flow with radionuclide scanning but are not functioning well enough to stop dialysis (Table 3), and are classed as failures in this analysis.

Fifty-two of the 65 (80.0%) patients are free of dialysis with a mean creatinine of 2.2 ± 1.2 (SD) mg/dL and blood urea nitrogen (BUN) of 37 ± 25 mg/dL. Kidney survival is 34 of 43 (79.1%) of primary grafts vs 18 of 23 (78.3%) after retransplantation (Table 3). Graft survival is 83.3% in the nonsensitized patients vs 73.3% in those who had preformed cytotoxic antibodies.

Rejection was the most frequent cause of graft loss (Table 3). The rate of this final diagnosis was about equal with primary grafting vs retransplantation (Table 3). However, the sensitized patients who were heavily represented in the retransplant group had irreversible rejection at three times the rate of patients without cytotoxic antibodies, particularly if there was a cytotoxic crossmatch (Table 3). The imbalance is even greater if the diagnosis is assumed to be rejection in the three patients with continuing dysfunctional grafts; two of the three were presensitized.

Rejection accounted for the loss of only three primary grafts with a negative crossmatch, one in a patient who also had sickle cell crises in the postoperative period. The other losses were in diabetic women. One, who lost her graft in 10 days, underwent successful retransplantation 5 months later. The second woman lost her graft after an unwise decision was made to reduce FK 506 by half 5 months postoperatively. She had a perfect result at the time, and was not on steroids.

Two of the graft losses in primary nonsensitized recipients were due to donor disease which was not recognized. In one, the aortic conduit for en bloc pediatric kidneys was found later to have had transmural necrosis pretransplantation, and clotted in less than 24 hours. A delayed peritoneal culture from another en bloc pediatric donor showed mixed bacteria. The recipient of the liver from this donor developed severe candida peritonitis within 72 hours. The kidney recipient developed a candida mycotic pseudoaneurysm, necessitating removal of the normally functioning graft and ligation of the iliac artery 32 days postoperatively. Recipient death accounted for the other primary graft loss after 2 days in a nonsensitized recipient. If these three nonimmunologic failures are excluded from the analysis, the graft loss rate in primary transplantation is 6 of 40 (15%) and in the nonsensitized recipients, it is 3 of 33 (9.1%).

Table 3. Graft Survival and Causes of Graft Loss

Graft Survival	Primary 34/43* (79.1%)	Retransplantation 18/23 (78.3%)	Nonsensitized 30/36 (83.3%)	Sensitized 22/30 (73.3%)
Graft loss	9/43 (20.9%)	5/23 (21.7%)	6/36 (16.7%)	8/30 (26.7%)
Rejection	5	3	2	6
Continuing dysfunction	2	1	1	2
Necrotic donor renal artery	1		1	
Mycotic pseudoaneurysm		1	1	
Death	1		1	

*Includes six patients with positive crossmatch.

Immunosuppressive Requirement

During most of the time of this pilot case compilation, the treatment protocol was not standardized. A 3- to 5-day course of 5 or 10 mg/d OKT3 was given after 18 of 66 (27.3%) transplantations. However, the reasons for this decision in preference to FK 506 or steroid augmentation were variable and sometimes not biopsy validated. Azathioprine maintenance therapy was never used. Consequently, the best judgment about the efficacy of FK 506 was based on how much prednisone was required to maintain stable graft function after the first 2 months. This information is given in Table 4 after follow-ups of 2.5 to 11 months. Of the 52 (80.0%) patients of the original 65 who have functioning grafts, 31 (59.6%) did not receive steroids, 8 (15.4%) more were on 2.5-5 mg/d, and 12 (23.1%) were taking 10-20 mg/d. One patient (1.9%) is taking 25 mg/d.

Infections

These are reported elsewhere at this meeting by Kusne et al.[4] The infectious profile was similar to that with past immunosuppressive regimens. However, lethal systemic sepsis was notably absent, possibly because of the limited use of steroids. Cytomegalovirus (CMV) was the most common infection and 8 of the 65 patients had clinical problems serious enough to be treated with Ganciclovir.

Table 4. Steroid Requirements in 52 Patients With Functioning Grafts (2.5 to 11 Months)

Prednisone Dose	No. of Patients (%)
0	31 (59.6)
2.5-5 mg/d	8 (15.4)
10-20 mg/d	12 (23.1)
25 mg/d	1 (1.9)

Table 5. Antihypertensive Medications in 52 Patients With Functioning Grafts

No. of Medications	No. of Patients (%)
0	21 (40.4)
1	24 (46.2)
2	5 (9.6)
3	2 (3.8)

Late Postoperative Risk Factors

Even in successful cases, renal transplant recipients historically have had a high incidence of complications which may impact negatively on the quality of life or the long-term prognosis. These were examined in the 52 patients who have functioning grafts.

Hypertension. Most of the patients who came to transplantation were taking antihypertensive medications. At present, 45 (86.6%) are free of these medications or on monodrug therapy (Table 5).

Hypercholesterolemia and Hyperuricemia. The serum cholesterol for the 52 patients is 172 ± 38 mg/dL (SD) (lower range of normal) and the mean uric acid levels are 7.8 ± 2.2 mg/dL (SD) (high range of normal).

New Diabetes Mellitus. Five of 52 (9.6%) patients with surviving grafts were not diabetic before transplantation, but needed chronic insulin therapy afterwards. This incidence is comparable to or lower than that reported for conventional immunosuppressive regimens.[5-7]

Neurotoxicity. Central and peripheral nervous system toxicity was evaluated systematically with the use of a questionnaire that was designed to elicit complaints of tremors, insomnia, headaches, light sensitivity, nightmares, hallucinations, tingling, and more serious manifestations such as convulsions or paralysis. The most common side effects were tremors, paresthesias of the hands and/or feet, and insomnia. These tended to be relatively minor and most patients did not spontaneously complain. Serious neurologic problems such as the expressive dysphasia which we reported in two liver recipients[8] were not seen.

DISCUSSION

These trials with renal transplantation came late and played a relatively minor role in the clinical introduction of FK 506 therapy which concerned mainly the liver.[9-11] However, the kidney trials have added to the impression that this is a safe drug to the extent that safety is possible with any powerful immunosuppressant. The mortality in the present trial was 1.5%, and the freedom from historical posttransplant morbidity was impressive. This was due largely to the ability to minimize or stop steroids within the first 2 months in 75% of cases. None of the kidney or nearly 500 other organ recipients treated with FK 506 was ever switched to another drug.

In earlier publications, we delineated the principal side effects of FK 506 as nephrotoxicity, neurotoxicity, and diabetogenicity.[12-14] Nephrotoxicity is not easy to define in the renal transplant model, but precise studies in heart and liver recipients are being reported.[15] It appears that the greatest risk of nephrotoxicity is during the early postoperative period when there is a tendency toward overdosage and consequent high blood levels while the drug is given IV.[16] Undoubtedly, improvements will be possible during this so-called induction. Afterwards, minor oral dose adjustments are easy to make, more or less guided by plasma trough levels. The supreme confounding factor in dose control is hepatic dysfunction.[16,17] The absence of severe hypertension, or the relief of this condition when it had predated transplantation is noteworthy.

The diabetogenic effects of FK 506 therapy have been similar to those seen in past regimens. Like CyA, FK 506 inhibits insulin release by pancreatic islets and it may increase peripheral insulin resistance.[18]

Similarly, neurotoxicity, while important to assess, follows the same general pattern as CyA. So far, serious neurotoxicity has been noted only in liver recipients.[8] This is not surprising since pathologic demyelinating changes in the brain stem caused by end-stage liver disease involve the same general anatomic regions as may be demyelinated by drugs like FK 506 and CyA.

As discussed elsewhere,[19] it is more than coincidence that both the desired qualities and side effects of FK 506 and CyA follow a similar pattern, in which the expression of details may be significantly different. However, hypercholesterolemia, hyperuricemia, and hypertension, which have been troublesome features of CyA regimens,[20] are not prominent features of FK 506. Whether this advantage is also related primarily to low steroid needs will be determined with further observations.

Comparisons of the therapeutic efficacy as well as the toxicity of FK 506 vs CyA undoubtedly will be clarified in the randomized trials that are now proceeding with hepatic and renal transplantation. At the moment, FK 506 appears to be the superior drug.

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