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# FK 506 Salvage of Renal Allografts With Ongoing Rejection Failing Cyclosporine Immunosuppression

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FK 506 is an experimental immunosuppressive drug that has been used with encouraging results as primary therapy in early clinical trials of renal transplantation.[1,2] In an early randomized trial comparing FK 506 and cyclosporine (CyA)-based immunosuppression, the major advantage of FK 506 appeared to be the ability to taper steroids, permitting FK 506 monotherapy, with no additional risk of rejection episodes in 60% of patients.[2] This is usually not possible with CyA-based immunosuppression because of both increased risk of rejection and nephrotoxicity.[3] The superior results observed with FK 506 may be due in part to its greater immunosuppressive potency compared to CyA.[4] These observations led us to evaluate FK 506 as a salvage agent to "rescue" renal allografts failing CyA-based therapy. We previously reported that FK 506 is unlikely to salvage renal allografts with chronic rejection or CyA toxicity.[5] However, conversion from CyA to FK 506 in failing grafts with ongoing acute rejection appeared to be much more promising, with graft salvage in 17 of 24 (71%) such cases.[5] We report herein our expanded experience with FK 506 conversion as "rescue" therapy for renal allografts with ongoing rejection failing CyA therapy.

## MATERIALS AND METHODS

### Patients

A total of 54 patients (30 male, 24 female) with a mean age of 33.7 ± 10.9 years (range 8 to 59 years) were failing CyA immunosuppression and were converted to FK 506. Forty-three patients had undergone primary transplantation and 11 had been retransplanted (8 second, 2 third, and 1 fourth transplants). Thirty-five were recipients of cadaveric (CAD) grafts and 19 were from living donors (15 related, 4 nonrelated).

### Evaluation for FK 506 Conversion

All 54 patients considered for conversion to FK 506 had uncontrolled rejection on primary CyA-based immunosuppression. Forty-one patients (76%) were referred to us from other centers where they were deemed to be losing their grafts; 13 patients (24%) were entered from our own institution. Prior to FK 506 conversion, maintenance immunosuppression consisted of CyA and prednisone in all patients, either with (n = 37) or without (n = 17) azathioprine (AZA). Previous treatment for rejection had been administered to all 54 patients in the form of bolus high-dose steroids; 37 patients (69%) had also received one (n = 28) or two (n = 9) courses of OKT3 prior to conversion. Fifteen patients (28%) received both OKT3 and antilymphocyte globulin (ALG) prior to FK 506.

All patients were evaluated by Doppler ultrasound and radionuclide flow study of the allograft to rule out a technical cause of allograft dysfunction prior to conversion. Core biopsies of the allograft were performed in all patients and revealed acute cellular rejection (ACR) in all cases; 13 of the biopsies also showed components of vascular rejection.

### Procedure for FK 506 Conversion

All 54 patients had received CyA doses maximized to tolerable levels. A simple switch ("clean conversion") from CyA to FK 506 was carried out in all cases by giving a standard daily oral dose of 0.3 mg/kg/d FK 506 in divided doses every 12 hours starting 12 hours after the last CyA dose. In addition, 14 patients received parenteral doses of FK 506 of 0.025 to 0.1 mg/kg/d overlapping with the first 1 to 4 days of oral therapy. Dose adjustments were based upon monitoring of trough serum FK 506 levels by ELISA[6] to achieve a 12-hour trough level of 1.0 to 2.0 ng/mL, and also by adjustment according to clinical and biochemical parameters. Data were analyzed for statistical significance by Student's *t* test and chi-square analysis where appropriate.

## RESULTS

FK 506 conversion was deemed successful contingent upon a return to baseline serum creatinine (SCr), and/or improvement on postconversion renal allograft biopsy, and/or freedom from dialysis if the patient was dialysis dependent at conversion. With a mean follow-up of 10.6 ± 7.3 months, success was achieved in 38 of 54 patients (70%) switched to FK 506 based on these criteria (Table 1). Of these, 9 patients (24%) had evidence of a vascular component of rejection on preconversion biopsy. Thirty-seven patients had failed at least one course of OKT3 (average length of treatment 11 days) and, of these, 15 had

**Table 1. FK 506 Conversion in 54 Renal Transplant Recipients Failing CyA Therapy**

| Indication for FK 506 Conversion | No. Patients (%) | No. Successful Conversions (%) |
|---|---|---|
| Acute cellular rejection | 34 (63%) | 26 (76%) |
| Vascular rejection | 13 (24%) | 9 (69%) |
| Acute cellular rejection with primary graft nonfunction | 7 (13%) | 3 (43%) |
| Total | 54 | 38 (70%) |

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also received induction ALG. In sum, of 38 patients receiving preconversion antilymphocyte preparations, 28 (74%) were salvaged with FK 506. Fifteen patients (28%) were already dialysis dependent prior to conversion to FK 506. Eight of these patients (53%) now have functioning grafts with a mean SCr of 1.86 ± 0.53 (mean follow-up 15 ± 8.3 months postconversion).

The median time to rescue with FK 506 for all 54 patients was 2 months (range 2 weeks to 36 months) after transplantation. In those patients successfully rescued, the mean SCr prior to FK 506 (excluding the eight patients on dialysis at conversion) was 3.3 ± 1.6 mg/dL which fell after FK 506 therapy to a mean of 2.4 ± 0.7 mg/dL ($P < .05$). Including the eight patients on dialysis at the time of conversion, the average SCr after FK 506 conversion was 2.3 ± 0.7 mg/dL. Salvage of cadaveric grafts (24 of 35, 69%) and grafts from living donors (14 of 19, 74%) was achieved with equal frequency. Those patients initially immunosuppressed with CyA, prednisone, and AZA (n = 37) experienced a superior success rate of 81% compared with 47% for those who had received CyA and prednisone alone (n = 17) preconversion ($P < .01$). Of 41 patients referred from other centers for FK 506 conversion, 31 (76%) were successfully rescued compared with 7 of 13 (54%) successes in patients from our own institution. Of the 43 primary transplantations, 30 (70%) were successfully converted; 8 of the 11 retransplants (73%) were successes. Four patients with kidney–pancreas transplants were converted with 3 successes (75%). Three patients undergoing FK 506 conversion had been transplanted with pediatric en bloc kidneys; 2 (67%) were successfully salvaged.

### Morbidity and Mortality

There were five deaths, all occurring in patients whose grafts had been lost. Two patients died from overwhelming sepsis and lymphoma at 1 month and 7 months postconversion, respectively. One patient died 8 months after conversion while on dialysis (etiology unknown), 1 from overwhelming sepsis at 1 month, and 1 patient succumbed to an intracranial hemorrhage 4 months after conversion. Eleven patients referred for FK 506 rescue had experienced prior complications including CMV gastritis in 4, urine leak requiring surgical correction in 3, perforated duodenal ulcer following high-dose steroid therapy for rejection in 1, ureteral obstruction in 1, herpesvirus infection (cutaneous) in 1, and *Candida esophagitis* in 1. Eight of these patients (73%) were subsequently successfully rescued with FK 506. There were 9 complications following FK 506 conversion including new onset diabetes mellitus in 2 patients (1 requiring insulin, 1 controlled on oral medication), epistaxis (n = 1), cecal perforation (n = 1), line sepsis (n = 1), disease recurrence (membranoproliferative glomerulonephritis, n = 1), proteinuria (n = 1), and bacterial pneumonia (n = 1). None of these complications could be directly related to FK 506 therapy and none resulted in mortality.

**Table 2. Steroid Therapy Before and After FK 506 Rescue**

| Prednisone Dose (mg/d) | No. Patients (%) | |
|---|---|---|
| | Preconversion | Postconversion |
| 0 | 0 (0%) | 6 (16%) |
| 5 | 0 (0%) | 5 (13%) |
| 7.5 | 0 (0%) | 6 (16%) |
| 10 | 5 (13%) | 13 (34%) |
| 12.5 | 1 (2.5%) | 3 (8%) |
| 15 | 1 (2.5%) | 2 (5%) |
| 20 | 21 (55%) | 2 (5%) |
| >20 | 10 (27%) | 1 (3%) |
| Mean dose | 21.3 ± 7.5 | 8.8 ± 6.2 |

### Immunosuppression and Biochemistry Following FK 506 Conversion

All patients successfully converted from CyA to FK 506 were taking prednisone prior to conversion (Table 2). Prednisone doses have been lowered from an average of 21.3 ± 7.5 mg/d preconversion to 8.8 ± 6.2 mg/d postconversion, and 6 patients (16%) are currently on FK 506 monotherapy. Mean cholesterol and triglycerides were 193 ± 28.5 and 221.8 ± 97.6 mg/dL preconversion and 181.2 ± 33.6 and 193.5 ± 96.8 mg/dL postconversion, respectively ($P$ = NS). In nondiabetics, glucose was 95.5 ± 16.7 mg/dL preconversion and 91.2 ± 15.7 postconversion ($P$ = NS). Serum uric acid was 7.2 ± 2.3 mg/dL and 7.0 ± 2.1 ($P$ = NS), respectively.

## DISCUSSION

Since the advent of CyA-based immunosuppression, the results of renal transplantation have improved markedly.[7–9] Unfortunately, the incidence of rejection episodes remains high even with multiple drug regimens based on CyA.[3] Treatment of persistent rejection with high-dose steroids and/or antilymphocyte preparations have until now been the only options open to the clinician faced with a failing graft under CyA-based therapy. These treatment strategies are not always successful and, of themselves, have high attendant morbidity. An alternative treatment for persistent graft rejection would be an important addition to the armamentarium of the transplant physician. FK 506 has shown great promise as a primary therapeutic drug in renal transplantation, and its use permits withdrawal of steroids in up to 60% of patients. This study illustrates another, perhaps even more important use for FK 506 as a therapeutic tool. In 38 of 54 (70%) patients losing their grafts to ongoing rejection, rescue therapy with FK 506 resulted in graft salvage. Twenty-eight of these 38 patients (74%) had already failed treatment with antilymphocyte preparations and all had previously received high-dose steroid therapy. Graft salvage by conversion to FK 506 was achieved with little, if any, morbidity. Steroid tapering

was still possible in the majority of patients successfully switched to FK 506, and no patient required subsequent treatment for recurrent rejection. Six patients have been taken off prednisone completely. Necessity for dialysis was not a preclusion for conversion to FK 506, as 8 of 15 such patients achieved graft function (mean SCr 1.9) following rescue.

The precise mechanisms by which FK 506 affects graft salvage as an "antirejection" agent is unclear. Another novel drug, RS-61443, has recently been reported to show promise in reversing ongoing rejection,[10] although with somewhat less success than that reported herein with FK 506. As alternative strategies to the more traditional methods of treating recalcitrant rejection are developed, improved long-term graft survival and reduced patient morbidity will hopefully be observed. The use of FK 506 to salvage renal allografts with ongoing rejection after failed CyA therapy appears to be a safe and effective means to help achieve these goals.

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