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# The Clinical Trial of FK 506 as Primary and Rescue Immunosuppression in Pediatric Cardiac Transplantation

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IN CONCERT with the adult trial of FK 506 begun in October 1989 at Presbyterian University Hospital, a similar trial to investigate the use of FK 506 as both primary and rescue immunotherapy was initiated in the pediatric population at Children's Hospital of Pittsburgh. In a prospective clinical trial 19 pediatric patients have undergone orthotopic cardiac transplantation with FK 506 and low-dose steroids as primary immunosuppression. Encouraging results have also been obtained in four children with refractory cardiac rejection who have undergone rescue therapy with FK 506.

## PATIENTS AND METHODS

### Patient Group

Nineteen patients were prospectively entered into this study from October 1989 to August 1991. Informed consent was obtained from each patient and family before transplantation for the use of FK 506 and steroids as the sole immunosuppressive therapy; two patients received conventional cyclosporine-based immunosuppression during this period.

In the study group were 14 males and 5 females (age range 5 days to 17 years). Four patients (21%) required mechanical circulatory support before transplantation in the form of Extra Corporeal Membrane Oxygenation (ECMO) (3) and Novacor Left Ventricular Assist Device (LVAD) (1). Nine (47%) other patients awaited transplantation with either ventilatory and/or inotropic support. Thus 13 (68%) of 19 patients were UNOS Status I at the time of transplantation. The etiology of cardiomyopathy included congenital heart disease (11), idiopathic (6), restrictive (1), and viral (1). Median follow-up of these 19 patients was 304 days (range 5 to 668 days) as of August 1991. No attempt was made to enroll patients selectively in this study based on severity of illness or preoperative status.

The 11 children with congenital heart disease in many ways represented the most challenging problems resulting from multiple prior operations and their anatomic constraints. The following is a list of the congenital disorders for which our pediatric group underwent transplantation and their respective ages: hypoplastic left heart syndrome (3) (5, 25, and 42 days); transposition of the great vessels (2) (2 and 17 years); single ventricle (2) (7 and 14 years); tricuspid atresia (2) (12 and 17 years); double inlet left ventricle and left AV valve atresia (1) (4 years), and cardiomyopathy following coarctation of the aorta and left ventricular outflow tract obstruction (1) (5 years).

Four pediatric patients who had cardiac rejection refractory to conventional immunosuppressive treatment were treated with FK 506 rescue therapy. Three of these patients were from our own institution and one was referred from an outside center.

### FK 506 Therapy

FK 506 was administered intravenously for 24 to 72 hours after cardiac transplantation at a dose of 0.075/mg/kg per day in two divided doses. Oral FK 506 was begun 24 hours after transplantation. The oral maintenance dose of FK 506 required to attain a level of 0.5 to 1.0 ng/mL (12 hour through serum ELISA by the technique of Temura)[1] has ranged from 0.2 to 0.4 mg/kg per day. Methylprednisolone, 7 mg/kg, was administered intravenously in the operating room and 5 mg/kg postoperatively for 24 hours in three divided doses. Thereafter, patients received 0.15 mg/kg per day prednisone orally once a day. Prednisone was then tapered and discontinued based on rejection history. All but three children have been tapered off all steroids within the first month posttransplant.

### Other Agents

All patients entered into the FK 506 immunotherapy protocol were placed on prophylactic oral trimethoprim/sulfamethoxazole, acyclovir, and Mycostatin.

### Monitoring for Rejection

Posttransplant surveillance on all patients involved weekly transvenous endomyocardial biopsies during hospitalization and at slowly increased intervals after discharge. The neonates were biopsied at 1- to 3-month intervals. Biopsies were graded using hematoxylin and eosin staining after light microscopy by a pathologist who was blinded to the immunosuppressive protocol of the patient. Biopsy grades were defined according to standardized nomenclature. Rejection was defined by the presence of myocyte necrosis in association with an interstitial lymphocytic infiltrate (grade 3 or moderate rejection) or with hemorrhage (grade 4 or severe rejection).

### Monitoring for Infection

All patients were followed by an infectious-disease specialist. Pretransplant titers for hepatitis B, herpes virus, Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), Toxoplasma, and cytomegalovirus (CMV) were performed on all donors and recipients. The diagnosis of infection was made using clinical criteria as previously defined by this institution.[2] Complete blood screening was performed daily in the hospital and at all follow-up visits. Questionnaires to identify untoward side effects of FK 506 were completed on all patients.

## RESULTS

### Survival

Seventeen of 19 (89%) patients entered into this trial are alive. There were no perioperative (30 days) deaths. There

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were two late deaths, one (90 days) secondary to sepsis in a child with preexisting lung disease and bronchiectasis who succumbed to pulmonary and disseminated cryptococcal infection. This child also suffered from severe cardiac cachexia with associated ascites, hypoalbuminaemia, and hypogammaglobulinaemia. His immunosuppression consisted of very low dose FK 506 without steroids, and no cardiac rejection occurred. The second death (120 days) was secondary to posttransplant lymphoproliferative disease (PTLD) and an associated disseminated CMV infection in a 6-year-old girl on FK 506 as her sole immunosuppressive agent. No mortality has been directly attributed to FK 506 therapy or to acute or refractory rejection.

### Rejection

At 3 months posttransplant there were 14 episodes of rejection (grade 3A or greater) in 19 patients, or 0.7 episodes per patient. Seven of these 14 episodes of rejection occurred in two patients, one of whom had a panel reactive antibody (PRA) of 55% and one other patient in whom FK 506 was administered at a very low dose due to a pretransplant creatinine clearance of 20 mL. The actuarial freedom from grade 3A rejection was 60% at 3, 6, and 9 months.

Rejection episodes of moderate severity (Billingham criteria 3A) were preferentially treated by increased doses of FK 506, 2 to 4 mg/d. Moderate or severe rejection (Billingham criteria 3B or 4) was treated either by intravenous methylprednisolone, 7 mg/kg for 24 or 48 hours, or with a short-course oral prednisone taper, 50 mg to 10 mg over 5 days, in those patients whose FK 506 levels were already in the high therapeutic range or in whom azotemia (BUN >50 and creatinine >2.0) limited further manipulation of FK 506 therapy.

The two patients mentioned previously in whom seven of the episodes of rejection occurred are the only two pediatric patients who have required the addition of azathioprine as additional immunosuppressive therapy. The young boy with the preexisting renal dysfunction was also treated with one course of OKT3.

### Infection

There were seven major infections in 4 of 19 patients (21%). One neonate with HLHS and a prolonged ICU course developed line sepsis (staphylococcal), peritonitis from a peritioneal dialysis catheter, and an episode of parainfluenza pneumonia; he has recovered well and is now over 1 year of age. A second neonate transplanted for HLHS had an uneventful perioperative course but returned 4 weeks later with candida sepsis secondary to pyelonephritis and has recovered following amphotericin therapy. Two deaths occurred with associated sepsis (see section on Survival above). One other child recovered from a CMV pneumonia following gancyclovir therapy.

There have been six minor infections in 5 (26%) of 19 patients. There were two varicella infections and three patients with sinusitis (two of which were sterile). A critically ill child following prolonged CPR and ECMO support developed CMV in the urine, which resolved with appropriate treatment.

### Cardiac Function

All surviving patients enjoy excellent cardiac function. The average left ventricular ejection fraction (LVEF) in the group measured by gated nuclear scan and/or echocardiography was 66%. The range of LVEF was 60% to 75% at the time of longest follow-up.

### Renal Function and Hypertension

FK 506 was extremely well tolerated in the pediatric group of cardiac transplant recipients. The average pretransplant serum creatinine was 0.7 ng/dL (std. err. 0.1) and at 3 months posttransplant was 0.9 ng/dL (std. err. 0.1). Moderate oliguria and transient azotemia was associated with the IV administration of FK 506 particularly if preexisting renal dysfunction was present. Two patients required temporary peritoneal dialysis; one patient had renal vein thrombosis secondary to IV lines and the other was in anuric renal failure pretransplant secondary to cardiac arrest. Normal renal function has returned in both of these patients.

Only two patients have required antihypertensive therapy. One patient remains on antihypertensive treatment and she was hypertensive prior to transplant. The other patient's blood pressure has normalized following repair of an aortic coarctation. Compared to the prior cyclosporine (CyA) era in which the incidence of hypertension was 70%, this represents a dramatic reduction in the necessity to treat hypertension posttransplant ($P < .001$).

### Cardiac Rescue Therapy

Four patients who suffered from cardiac rejection refractory to aggressive conventional immunotherapy were treated with FK 506. All of these patients had been treated with CyA, azathioprine, and steroids; all had received two or more courses of intravenous steroids and one or more courses of antilymphocyte therapy (RATG, Minnesota ALG, or OKT3) and had persistent rejection.

The rescue patients tolerated the switch from CyA to FK 506 without significant complications. Cyclosporine was discontinued 24 to 48 hours prior to FK 506 induction. No loading dose of FK 506 was administered. The patients were begun on oral FK 506, 0.3 mg/kg per day, in two divided doses. Azathioprine was discontinued and steroids were given at half the maintenance dose. Pending improvement in subsequent biopsies, steroids were tapered and all eight patients are on one-quarter their previous prednisone dose. All patients have either resolved or significantly improved the histologic endomyocardial biopsy grading of rejection. One rescue patient died of suicide.

### Metabolic Studies and Side Effects

No pediatric patient on primary or rescue FK 506 immunotherapy has required insulin therapy or had abnormal fasting blood sugars. Continued monitoring of hematologic and coagulation indices, as well as hepatic function, failed to reveal any abnormalities in our patients at this follow-up interval. Cholesterol and triglycerides have been slightly lower than those in CyA-treated patients; however, this was not statistically significant. Four patients had borderline elevated uric acid levels. Slightly elevated serum potassium levels have also been observed in some patients, independent of renal dysfunction, and we have avoided the exogenous administration of potassium in this group unless specifically indicated (serum $K^+$ <3.5 mEq/L). Anemia (hematocrit <28) has been problematic in almost 30% of the children on FK 506. One of these children had an associated parvovirus infection to which the anemia could be attributed. The other five children have had completely normal anemia studies including bone marrow biopsies. This anemia is associated with low erythropoietin and reticulocyte levels and has responded well to erythropoietin therapy. Further evaluation of the mechanism of this anemia is under study.

Side effects have been rare despite routine questionnaires during hospitalization and during outpatient follow-up. There have been no seizures, cerebrovascular accidents (CVA), or neuropathies secondary to FK 506. One patient in the primary therapy group had an intracerebral hemorrhage and seizure from which she recovered with little residual deficit. There have been occasional reports of extremity paresthesia and temperature malsensations usually associated with elevated FK 506 levels. Muscle aches and mild insomnia were also reported rarely. Notably absent in this patient group were complaints of gingival hyperplasia, tremor, or hirsutism.

## DISCUSSION

The results from this prospective trial of FK 506 as immunotherapy in pediatric patients following cardiac transplantation have been dramatic. The pediatric population, previously the more problematic group in terms of rejection and hypertension when compared to the adult group during the CyA era, has become relatively easy to manage. As a way of illustrating the dramatic improvement realized in this pediatric cardiac transplant group, the actuarial freedom from grade 3A rejection at 3 and 6 months posttransplant on FK 506 was 60% vs 20% and 12%, respectively, for the 15 children transplanted prior to the use of FK 506 on CyA/azathioprine/steroids ($P < .001$). Equally impressive, but not apparent in these statistics, is that only 20% of the children in the FK 506 group were on steroids at these follow-up intervals vs 100% of the CyA group who remained on high-dose steroids. This level of immunosuppression has been attained without antilymphocyte therapy, without immunoprophylaxis, without azathioprine, and with marked reduction in steroid requirement. As further evidence of the potency and selectivity of the immunosuppressant effects of FK 506 it has been more difficult to propagate lymphocytes from endomyocardial biopsies from patients treated with FK 506 than those previously treated with CyA triple-drug therapy, particularly at higher histologic grades. Another added advantage of FK 506 is the flexibility it introduces to immunosuppressive management. Mild to moderate rejection that occurred was preferentially treated merely by increasing the resting level of FK 506. The concept of augmenting immunosuppression and thereby treating rejection by increasing baseline immunotherapy introduces a new tool to our armamentarium of antirejection therapy.

Side effects and toxicity have been few. Renal dysfunction has been minimal. Hirsutism, gingivitis, and facial bone growth abnormalities associated with CyA have not been observed. Annual catheterizations performed to date have failed to reveal any coronary abnormalities. The marked diminishment in steroid requirement will undoubtedly hold promise for improved growth potential and diminished obesity, hyperlipidemia, hypertension, and cushingoid habitus.

We are continuing to learn about appropriate FK 506 dosing and levels. Clearly, this is a potent immunosuppressive agent, and during our early experience moderate overdosing occurred. We feel the initial IV loading dose is important to initiate the highly specific effects of this agent and to prevent up-regulation of the immune system. However, the initial dose should be limited to 0.075 mg/kg per day as a continuous infusion for 24 hours and then discontinued. In children, lower levels of FK 506 produce comparable or superior results to that seen in adults. Levels of 0.4 to 1.0 ng/mL are therapeutic in children.

Cardiac function and the quality of these children's lives have been excellent. We are extremely encouraged by the dramatic immune advantage this agent seems to hold for the young patient facing cardiac transplantation and a future wedded to immunosuppression. We are hopeful that the tremendous advantage observed in this preliminary study is borne out by more long-term follow-up.

## REFERENCES

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