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HEART TRANSPLANTATION

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

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FK 506, a potent immunosuppressive macrolide antibiotic, has undergone clinical testing at the Presbyterian University Hospital since January 1989. The initial clinical trials were directed at liver transplant recipients with refractory rejection,[1,2] and pursuant to these dramatic and gratifying results FK 506 was introduced as primary immunosuppression in kidney and liver recipients in March 1989.[3,4] Ever since October 1989, in a prospective clinical trial, 61 patients have undergone orthotopic cardiac transplantation with FK 506 and low-dose steroids as primary immunosuppression. Dramatic results were also attained in eight patients with cardiac rejection refractory to all known conventional treatment and who underwent rescue therapy with FK 506.

METHODS

Patient Group

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

In the study group were 53 males and 8 females (age range 18 to 61 years). Seven patients (11%) required mechanical circulatory support prior to transplantation in the form of the Novacor Left Ventricular Assist Device (LVAD) (5), Thoratec LVAD (1), and Total Artificial Heart (1). Six other patients awaited transplantation with intra-aortic balloon pump (IABP) support. The etiology of cardiomyopathy included ischemic (30), idiopathic (18), valvular (3), myocarditis (3), hypertrophic (3) and retransplantation (4). Median follow-up of these 61 patients was 260 days (range 15–670 days) as of August 1991. No attempt was made to enroll patients selectively in this study based on severity of illness or preoperative status.

Eight adult patients who had cardiac rejection refractory to conventional immunosuppressive treatment were treated with FK 506 rescue therapy. Four of these patients were referred to our institution from other centers.

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 1 to 1.5 ng/mL (12 hour through serum ELISA by the technique of Temura)[5]; it 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.

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. 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 a modified Billingham scale. 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.[6] 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.

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RESULTS

Survival

Fifty-six (92%) of 61 patients entered into this trial are alive. The earliest death occurred on the fourth postoperative day secondary to pulmonary hypertension and right-heart failure. Two other deaths occurred at 30 and 54 days from causes unknown; neither of these latter two patients had any episode of rejection. One patient died of sudden death at home on an exercise cycle and permission was denied for postmortem examination. The other patient died of low cardiac output, the etiology of which remains unclear despite complete postmortem examination; no evidence of cellular or humoral rejection was evident in the heart. Two late deaths have occurred, one due to infection and one due to coronary occlusion. No mortality has been attributed to FK 506 therapy or to acute or refractory cardiac rejection.

Rejection

At 3 months posttransplant there were 48 episodes of grade 3A rejection in 61 patients. Beyond 3 months few episodes of rejection have occurred. The episodes of grade 3A rejection at 90 days in this study were 0.8 per patient (n = 53). The actuarial freedom from rejection at 3 months was 40% and remained so at 6 and 9 months.

Rejection episodes of moderate severity (Billingham criteria 3A) were preferentially treated by increased doses of FK 506, 4 to 8 mg/d in the adult patients. Moderate or severe rejection (Billingham criteria 3B or 4) was treated either by intravenous methylprednisolone, 1 g for 24 or 48 hours, or with a short-course oral prednisone taper, 100 mg to 20 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.

Eight patients have required the addition of azathioprine to their immunosuppressive regimen and three patients have required treatment with OKT3 for severe rejection.

Infection

Three major infections in two patients were present prior to cardiac transplantation. One patient had two pretransplant infections: staphylococcal line sepsis secondary to an IABP, and a positive sternal wound culture for candida at the time of Novacor LVAD removal. This same patient had pulmonary emboli and infarctions yet remained free of infection posttransplant managed on FK 506 as his sole immunosuppressive agent. Amphotericin was administered for 5 weeks after transplantation and the patient recovered without sequelae. The other patient with a pretransplant infection had a Klebsiella pneumonia during IABP support, which had been treated for 8 days when a donor heart became available. This patient recovered without further infection.

At posttransplant there were 16 infections in 14 of 61 patients on primary FK 506 therapy. No patient in the rescue group had a diagnosed infection. There were six (10%) major infections in four patients, which consisted of three pneumonias, one pulmonary abscess, one *Clostridia difficile* colitis, and one abdominal wall and mediastinal infection after Novacor LVAD. There were 10 (16%) minor infections. Freedom from major infection in the primary FK 506 group at the median follow-up of 260 days was 90%.

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 48% to 75% at the time of longest follow-up.

Renal Function and Hypertension

In 53 patients followed for greater than 90 days the average serum creatinine prior to transplant was 1.2 ng/dL. When FK 506 was administered intravenously at a dose of 0.15 mg/kg per day infused either as bolus therapy twice a day or as a continuous 24-hour infusion there was associated nephrotoxicity. Three patients (5%) required dialysis in the perioperative period; however, renal function returned near baseline within 7 to 10 days. One patient who required dialysis suffered a cardiac arrest on induction to anesthesia and had an IABP inserted; these events were associated with mild hepatic dysfunction and FK 506 levels greater than 20 ng/mL in the early posttransplant period. Since IV induction FK 506 has been changed to a continuous infusion dose of 0.075 mg/kg per day for 24 hours, acute renal dysfunction, which required dialysis, has not been observed. Excluding these three patients who required dialysis, peak renal dysfunction occurred at the first postoperative week, and the average serum creatinine was 2.6 ng/dL (standard deviation 1.03). This peak renal dysfunction was associated with an average FK 506 level of 5.1 ng/mL (range 0.8–12 ng/mL). The average serum creatinine at 3 months follow-up was 1.96 ng/dL (standard deviation 0.86) and was attained by most patients by the second postoperative week. Average serum creatinine at 6 months was 2.2 ng/dL.

Hypertension is rare in patients following cardiac transplantation treated with FK 506 and low-dose steroids. Only 22 patients (39%) followed for greater than 3 months have required antihypertensive treatment and all are well controlled on a single agent.

Cardiac Rescue Therapy

Eight patients who suffered from cardiac rejection refractory to aggressive conventional immunotherapy were treated with FK 506. All of these patients had been treated with cyclosporine (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 have 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 patient 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.

Two FK 506 rescue patients complained of muscle and joint aches and lower limb paresthesias for the first few weeks following the switch in therapy. These have all resolved. Presumably, these symptoms were related to CyA/FK 506 interactions as they have not been observed in primary FK 506 patients. Renal function has remained normal in all rescue patients.

Metabolic Studies and Side Effects

There were 11 insulin-dependent diabetics in the 56 patients on primary FK 506 therapy following cardiac transplantation. Four of these 11 diabetics were insulin dependent prior to transplantation. There were seven new-onset diabetic patients of 52 nondiabetic recipients (13.4%). All of the new-onset diabetics were also on prednisone (average dose 7 mg/d).

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 is not statistically significant. Four patients have 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).

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 a thromboembolic occipital CVA with associated hemorrhage and seizure from which he has recovered with little residual deficit. There have been occasional reports of extremity paresthesia and temperature malsensations usually associated with elevated FK 506 levels. One patient with mild multiple sclerosis developed akinetic mutism on FK 506, which required reduction in dosing; however, he has since recovered and returned to work. Muscle aches and mild insomnia were also reported rarely. Notably absent in this patient group were complaints of gingival hyperplasia, tremor, or hirsutism.

DISCUSSION

These preliminary results with FK 506 and low-dose steroid immunosuppression hold tremendous promise for the future, as both primary immunotherapy in cardiac transplantation and as an effective agent for rescue therapy in refractory cardiac rejection. In a prospective randomized study performed at the University of Pittsburgh, comparing RATG to OKT3 immunoprophylaxis, with CyA-based triple drug therapy, the OKT3 immunoprophylaxis group had an actuarial freedom from rejection at 90 days posttransplant of 40% with 1.0 episode of rejection per patient.[7] The actuarial freedom from rejection in the FK 506 and low-dose steroid immunotherapy group at 90 days posttransplant is 40% with 0.80 episodes of rejection per patient. We have been impressed with the ability of this new agent to attain comparable immunosuppression in cardiac transplant recipients to one of the best immunosuppressive protocols at the University of Pittsburgh during the last decade. This level of immunosuppression has been achieved without antilymphocyte therapy, without immunoprophylaxis, without azathioprine, and with marked reduction in steroid requirement. Seventeen of the 56 patients in this study are on no steroids at all. The average steroid dose in the adults is 8.6 mg of prednisone/patient. The ability of FK 506 to reverse cardiac rejection that has been refractory to aggressive treatment with conventional immunotherapeutic tools, along with the relatively low rate of major (11%) and minor (16%) infections, is further testament to the potency and selectivity of its immunosuppressive actions. Another added advantage of FK 506 is the flexibility it introduces to immunosuppressive management. Mild to moderate rejection, which occurred in the first 3 months posttransplant, was treated by merely increasing the FK 506 dose. The concept of augmenting immunosuppression and treating rejection by increasing baseline immunotherapy adds a new tool to our armamentarium of antirejection therapy. The biologic and immunologic basis for this quality of FK 506 is presently under intense study at the University of Pittsburgh.

Despite the excellent tolerance of FK 506 by patients, and few observed or reported side effects, renal dysfunction is a price paid when the drug is used as described in this report. We believe that systematic overdosing has occurred in patients receiving FK 506 intravenously in the perioperative period in our attempt to achieve high early FK 506 levels. We have changed initial bolus intravenous FK 506 therapy to continuous infusion, and now, more recently, we have lowered the initial IV dose to a single 24-hour constant-infusion dose at 0.075 mg/kg, with enteral FK 506 begun on the first postoperative day. When reduction or elimination of the postoperative IV loading dose of FK 506 was attempted, the time to the first grade 3 rejection was diminished to 22 days. We feel that the IV induction dose is important to gain appropriate early up-regulation of the immune system. Further refinements

in our knowledge regarding FK 506 dosing and therapeutic levels, together with the diminished incidence of hypertension, may actually improve the long-term outlook for renal function in cardiac transplant recipients. When compared to the 40 cardiac transplant recipients transplanted at the University of Pittsburgh before October 1989, the incidence of hypertension was 70% as opposed to 38% in the FK 506 group ($P < .01$). Twenty annual catheterizations have been performed, none of which revealed coronary disease.

Both cardiac function and the quality of life[8] in our small patient group have been excellent. Concerns regarding vasculitis and neuropathy have not been realized. The benefit of steroid sparing, lack of nonspecific bone marrow suppression, and antilymphocyte and antihypertensive therapy hold tremendous promise for the future of cardiac transplant recipients.

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