A decade (1982 to 1992) of pediatric cardiac transplantation and the impact of FK 506 immunosuppression

The decade from 1982 through 1992 witnessed tremendous growth in pediatric cardiac transplantation. At Children's Hospital of Pittsburgh 66 cardiac transplants were performed during this period (age range 7 hours to 18 years). The cause of cardiomyopathy was congenital ($n = 30$), cardiomyopathy ($n = 29$), myocarditis ($n = 2$), doxorubicin toxicity ($n = 2$), ischemic ($n = 1$), valvular ($n = 1$), and cardiac angiosarcoma ($n = 1$). Nine children (14%) required mechanical circulatory support before transplantation: extracorporeal membrane oxygenation ($n = 8$) and Novacor left ventricular assist system ($n = 1$) (Baxter Healthcare Corp., Novacor Div., Oakland, Calif.). The mean follow-up time was 2 years (range 4 months to 8 years). The overall survival in the group was 67%. In children with congenital heart disease (>6 months of age) the perioperative (30 day) mortality was 66% before mid-1988 ($n = 10$) and 0% since mid-1988 ($n = 11$). The late mortality (>30 days) in children with cardiomyopathy transplanted prior to mid-1988 was 66% ($n = 14$) and 7% since mid-1988 ($n = 15$). Since mid-1988 1- and 3-year survival was 82% in children with congenital heart disease and 90% in children with cardiomyopathy. Twenty-six children have had FK 506 as their primary immunosuppressive therapy since November 1989. Survival in this group was 82% at 1 and 3 years. The actuarial freedom from grade 3A rejection in the FK group was 60% at 3 and 6 months after transplantation versus 20% and 12%, respectively, in the 15 children operated on before the advent of FK 506, who were treated with cyclosporine-based triple-drug therapy ($p < 0.001$, Mantel-Cox and Breslow). Twenty of 24 children (83%) in the FK 506 group are receiving no steroids. The prevalence of posttransplantation hypertension was 4% in the FK 506 group versus 70% in the cyclosporine group ($p < 0.001$, Fisher). Renal toxicity in children treated with FK 506 has been mild. Additionally, eight children have been switched to FK 506 because of refractory rejection and drug toxicity. FK 506 has not produced hirsutism, gingival hyperplasia, or abnormal facial bone growth. The absence of these debilitating side effects, together with the observed immune advantage and steroid-sparing effects of FK 506, hold tremendous promise for the young patient facing cardiac transplantation and a future wedded to immunosuppression. (J THORAC CARDIOVASC SURG 1993;105:464-73)

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The decade from 1982 to 1992 has witnessed tremendous growth in pediatric cardiac transplantation. The initial cautious application of heart transplantation in children has greatly expanded to include infants, children with complex congenital heart disease and multiple palliative procedures, as well as children at high risk because of pulmonary vascular disease and those requiring mechanical circulatory support. Children with cardiomyopathies of unusual cause such as cardiac tumor, doxorubicin toxicity, Chagas' disease, carnitine deficiency, and myocarditis have benefited, as well, from transplantation. The technical challenges and infectious and immunologic risks, which are magnified in the pediatric heart recipient, have been largely overcome, such that the child can now anticipate 80% to 90% survival at the first year after transplantation. Since our initial report on pediatric heart transplantation in 1988,[1] perioperative and late mortality have declined dramatically, at a time when our candidate group has become increasingly high risk. In addition, beginning in November 1989, the clinical trial of FK 506 immunosuppression for pediatric heart transplant recipients was initiated at Children's Hospital of Pittsburgh. We report here our experience with this potent macrolide immunosuppressant, as well as our results in the 66 pediatric cardiac transplant recipients during the past decade.

Patients and methods

Patient group. Sixty-six children, age range 7 hours to 18 years, underwent cardiac transplantation from February 1982 to April 1992. There were 40 boys and 26 girls. The causes of cardiomyopathy were congenital heart disease ($n = 30$) (Table I), cardiomyopathy (idiopathic, hypertrophic, and restrictive) ($n = 29$), myocarditis ($n = 2$), doxorubicin toxicity ($n = 2$), ischemic ($n = 1$), valvular ($n = 1$), and cardiac angiosarcoma ($n = 1$). Nine patients (14%) required mechanical circulatory support before transplantation: Extracorporeal membrane oxygenation (ECMO) was used to support eight patients and a Novacor left ventricular assist system (LVAS) (Baxter Healthcare Corp., Novacor Div., Oakland, Calif.) was used in one other patient, 14 years of age. The mean follow-up was 2 years (range 4 months to 8 years).

FK 506 patient group. Twenty-six children (age range 7 hours to 18 years) have been enrolled in the study of FK 506 immunosuppression after cardiac transplantation. There were 16 boys and 10 girls. The causes of heart failure were cardiomyopathy ($n = 10$) and congenital heart disease ($n = 16$) (Table I). Eleven patients (42%) were supported with mechanical ventilation and/or inotropic agents before transplantation. Five patients (26%) required mechanical circulatory support: ECMO was used in four patients and a Novacor LVAS in one patient. All children with congenital heart disease in the FK 506 group had prior cardiac or thoracic surgical procedures (average of 2.3 operations per patient). The mean follow-up time in the group was 405 days.

Operation. Forty-five orthotopic cardiac transplants with moderate hypothermic cardiopulmonary bypass[2] and one heterotopic procedure[3] were performed. Eight children with hypoplastic left heart syndrome (HLHS) required profound hypothermia, circulatory arrest, and aortic reconstruction. Two children with HLHS had additional congenital cardiac repairs; one child had total anomalous pulmonary venous return and the other had an interrupted right-sided aortic arch. Ten children required pulmonary arterioplasty, end-to-end pulmonary arterial anastomoses, end-to-end vena caval anastomoses, or a combination of these, to reconstruct their anomalies. One of these children, with situs ambiguus and single ventricle, required inferior vena caval baffling as well. There were four second transplantations.

Table I. *Types of congenital heart disease*

	Cyclosporine and FK 506	*FK 506*
HLHS	8	5
HLHS and TAPVR	1	1
HLHS and right interrupted aortic arch	1	1
Single ventricle	6	4
Tetralogy of Fallot	3	1
Transposition of great arteries	3	1
Tricuspid atresia	3	2
Ventricular septal defect	2	—
Coronary artery anomaly	2	—
Aortic coarctation and LVOTO	1	1
Total	30	

HLHS, Hypoplastic left heart syndrome; *TAPVR*, total anomalous pulmonary venous return; *LVOTO*, left ventricular outflow tract obstruction.

Immunosuppression. All children, from 1982 until November 1989, received cyclosporine-based immunosuppression. Initially, cyclosporine was used with steroids alone, then with triple-drug therapy (cyclosporine, azathioprine, and steroids), and finally with rabbit antithymocyte globulin immunoprophylaxis and triple-drug therapy. Cyclosporine was begun during the postoperative period, enterally, 5 mg/kg per day, in two divided doses. The maintenance dose of cyclosporine varied from 4 to 20 mg/kg per day to maintain a whole-blood radioimmunoassay cyclosporine level from 500 to 700 ng/ml or 150 to 250 mg/ml by high-performance liquid chromatography. Steroids and azathioprine were begun before transplantation and continued after transplantation. On the basis of each child's rejection history, steroid weaning was begun at 6 to 12 months after transplantation.

Since November 1989, a prospective study with FK 506 and low-dose steroids was begun in children after heart transplantation. Informed consent was obtained from each family and 26 children have now been treated with this agent. Methylprednisolone, 10 mg/kg, was administered intravenously in the operating room and 7 mg/kg per day in three divided doses during the first day after transplantation. Thereafter, prednisone, 0.1 mg/kg per day, was given orally and discontinued after the first normal findings on endomyocardial biopsy. FK 506 was begun in the intensive care unit after transplantation, 0.05 mg/kg per day intravenously, as a continuous infusion, until gastrointestinal function returned. Oral FK 506, 0.3 mg/kg per day in two divided doses, was begun 24 to 48 hours after transplantation. The oral dose of FK 506 to maintain a 12-hour trough level of 0.2 to 0.8 ng/ml (serum enzyme-linked

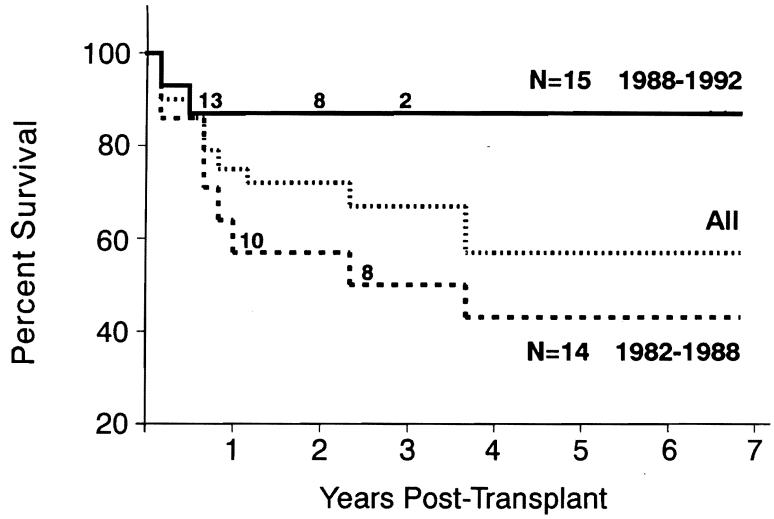

Fig. 1. Survival in pediatric heart transplantation in children with cardiomyopathy, $n = 29$: *1982-1988*, lower one-sided Brookmeyer-Crowley 95% confidence limit for median survival time = 7.57 months; *1988-1992*, Brookmeyer-Crowley 95% confidence interval not calculable; *all*, lower one-sided Brookmeyer-Crowley 95% confidence limit for median survival time = 27.77 months.

immunosorbent assay by the technique of Tamaura and colleagues[3]) has ranged from 0.2 to 0.4 mg/kg per day.

Monitoring and treatment for rejection. Posttransplantation surveillance on all patients involved weekly transvenous endomyocardial biopsies during hospitalization and at slowly increased intervals after discharge. The neonatal patients underwent biopsy at 1- to 3-month intervals. Biopsy specimens were graded by means of hematoxylin and eosin staining and light microscopy by a pathologist who was blinded to the immunosuppressive protocol of the patient. Biopsy grades were defined according to standardized nomenclature.[4] Rejection was defined by the presence of myocyte necrosis in association with an interstitial lymphocytic infiltrate (grade 3A or 3B, moderate rejection) or with hemorrhage (grade 4, or severe rejection). Grade 3A or 3B rejection was treated with intravenous methylprednisolone, 5 mg/kg per day, for 3 days. Grade 4 rejection was treated with rabbit antithymocyte globulin or OKT3.

Monitoring for infection and prophylaxis. All patients were followed up by a specialist in pediatric infectious disease. Pretransplantation titers for hepatitis A, B, C, and D, herpesvirus, Epstein-Barr virus, varicella, human immunodeficiency virus, *Toxoplasma*, and cytomegalovirus (CMV) were performed on all donors and recipients. If the date of transplantation was more than 1 month after the initial visit, any serologic tests with negative results were repeated. An intermediate-strength tuberculin skin test, along with an anergy panel, was also applied.

Perioperative antibiotic coverage consisted of intravenous cefamandole and was maintained for 48 hours in recipients older than 6 months of age. Neonatal recipients received ampicillin and cefotaxime. Since 1989, our prophylactic strategy for CMV has included intravenous ganciclovir for 4 weeks, followed by acyclovir (650 mg/m^2 per day) for 6 months. Only CMV-negative blood products were administered. Oral mycostatin and trimethoprim sulfamethoxazole were given to all patients after their transplant operation. Serologic follow-up for CMV, hepatitis, human immunodeficiency virus, Epstein-Barr virus, and toxoplasmosis was performed on all patients, both those who had seronegative studies at the time of transplantation and in seropositive patients to monitor for evidence of reactivation. Additionally, patients with fever episodes had cultures obtained from the blood, nasopharynx or throat, and urine for bacterial, fungal, and viral infection. More invasive procedures to obtain cultures were guided by the clinical presentation. The diagnosis of infection was made from clinical criteria as previously described.[5, 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.

Results

Survival and mortality

Cardiomyopathy. In the 29 patients with idiopathic, hypertrophic, and dilated cardiomyopathy the survivals at 1 and 5 years were 74% and 63%, respectively. The perioperative (<30 days) mortality for this group was 10%. Fourteen patients with cardiomyopathy underwent transplantation from February 1982 to June 1988 (early) and 15 patients with cardiomyopathy underwent transplantation from July 1988 to March 1992 (late). The perioperative mortality was 14% versus 6% in the early and late groups, respectively. However, the late mortality (>30 days) was 66% in the early group and only 7% in the late group. The major cause of late death in the early group (6/10) was rejection. The overall survival in the early group was 28% at 7 years and in the late group, 87% at 4 years after transplantation (Fig. 1).

Congenital heart disease. In the 21 patients with congenital heart disease who were 6 months and older, the

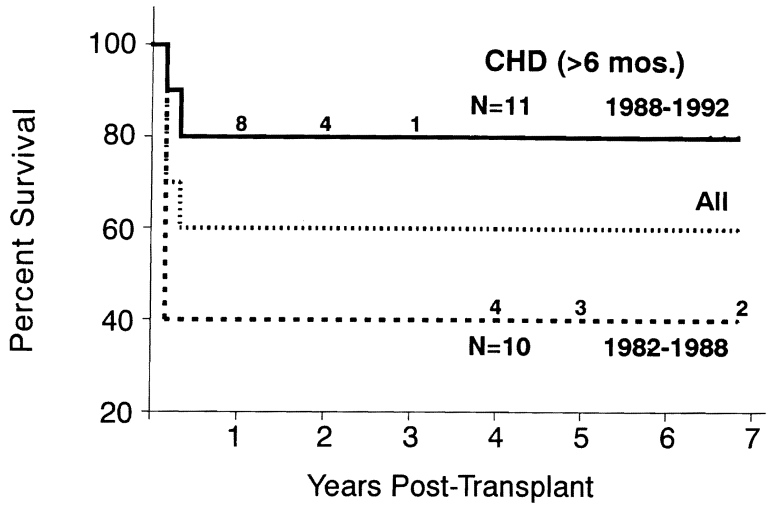

Fig. 2. Survival in pediatric heart transplantation in children with congenital heart disease (*CHD*), $n = 21$: *1982-1988*, lower one-sided Brookmeyer-Crowley 95% confidence limit for median survival time = 0.03 months; *1988-1992*, Brookmeyer-Crowley 95% confidence interval for median survival time is not calculable; *all*, lower one-sided Brookmeyer-Crowley 95% confidence limit for median survival time = 2.90 months.

survival at 1 and 5 years was 62%. The perioperative mortality was 35%. Ten patients underwent transplantation during the early period and 11 during the late period. The perioperative mortality was 60% in the early group and 0% in the late group. The major cause (5/6) of perioperative mortality was donor organ dysfunction and pulmonary vascular disease. The late mortality was 0% versus 18% in the early and late groups, respectively. In the early group with congenital heart disease, 2 of 10 children were supported by ECMO before transplantation and 8 of 10 children had an average of 1.1 prior cardiac or thoracic operations. In the more recent group of children with congenital heart disease, 2 of 11 children were supported by ECMO before transplantation and 11 of 11 children had an average of 2.3 prior cardiac or thoracic operations. The overall survival in the early group was 40% at 7 years and in the late group, 82% at 4 years after transplantation (Fig. 2).

FK 506 immunosuppression. Twenty-six children were treated with FK 506 immunosuppression after cardiac transplantation. The survival in the group was 82%. There were two early deaths (<30 days) resulting from respiratory distress syndrome ($n = 1$) and pulmonary vascular disease ($n = 1$). The perioperative survival was 92%. There were two late deaths due to infection ($n = 1$) and posttransplantation lymphoproliferative disease ($n = 1$) (Fig. 3).

Other. Nine children less than 6 months of age with HLHS underwent cardiac transplantation and aortic reconstruction. One child was delivered by cesarian section after the identification of a suitable organ donor at 35 weeks' gestation. Fetal lung maturity was determined by amniocentesis. The child required mechanical ventilation and cardiac catheterization soon after delivery because of the association of total anomalous pulmonary venous return with HLHS. She was discharged to her home after a 12-week hospitalization but died of an influenza pneumonia shortly thereafter. HLHS was diagnosed in utero in two other children and they were listed, as fetuses, for cardiac transplantation; both patients underwent transplantation after normal vaginal delivery. One of these children had an interrupted right-sided aortic arch in association with HLHS. The overall survival in this neonatal group was 66%.

Seven children had unusual cardiomyopathies: myocarditis ($n = 2$), doxorubicin toxicity ($n = 2$), ischemic ($n = 1$), valvular ($n = 1$), and cardiac angiosarcoma ($n = 1$). The perioperative survival in this heterogeneous group was 86%, however, two late deaths resulting from recurrent tumor (cardiac angiosarcoma at 10 months) and (gastrointestinal bleeding in a patient with human immunodeficiency virus and hemophilia) led to an overall survival of 57%.

Mechanical circulatory support. Nine children (age range 4 to 14 years) required mechanical circulatory support before transplantation because of postcardiotomy pump failure ($n = 4$) and cardiomyopathy or myocarditis ($n = 5$). Eight children were supported with ECMO for 3 to 8 days in the intensive care unit before transplantation. Three of these children are of particular interest:

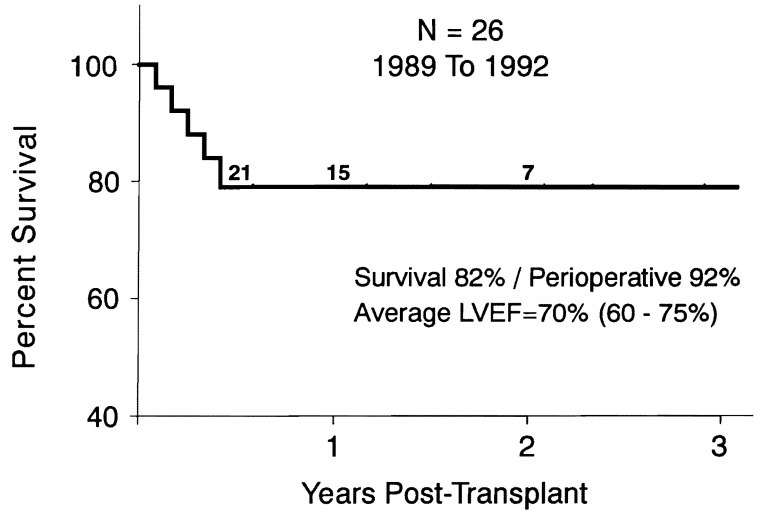

Fig. 3. Pediatric heart transplantation patient survival in pediatric heart transplantation on FK 506 immunosuppression, $n = 26$. Brookmeyer-Crowley 95% confidence interval for median survival time is not calculable. *LVEF*, Left ventricular ejection fraction.

One 5-year-old child with myocarditis was supported by ECMO after cardiac arrest and 90 minutes of cardiopulmonary resuscitation. His post-shock state was complicated by coma, anuric renal failure, and hepatic insufficiency. He was supported by ECMO for 72 hours before cardiac transplantation. In addition, he required 3 days of ECMO support after transplantation because of respiratory distress syndrome. This child is doing well, 1 year after transplantation, and has normal neurologic, renal, and hepatic function. Two other children supported by ECMO required percutaneous transatrial septostomy to decompress the left atrium and relieve pulmonary vascular congestion (Fig. 3). The ninth child, who had idiopathic dilated cardiomyopathy, was 14 years of age and was supported with a Novacor LVAS in conjunction with a centrifugal right ventricular assist system (RVAS). Three days after implantation, the RVAS was removed and the patient was eventually transferred to an out-of-hospital, philanthropic, "Family House" setting approved by the Food and Drug Administration. During this patient's 4-month wait for transplantation he required mantle radiation treatment for occult stage I nodular sclerosing Hodgkin's disease, diagnosed at the time of LVAS implantation. This patient is disease free and doing well 2 years after transplantation. The perioperative survival in this mechanical circulatory support group was 78%; however, two late deaths caused by respiratory distress syndrome ($n = 1$) and posttransplantation lymphoproliferative disease ($n = 1$) contributed to an overall survival of 56% in this group. The perioperative survival in patients receiving mechanical circulatory support in the early period (before July 1988) was 33% (1/3) compared with 100% in the late period (after June 1988). There was one late death during each period, such that the overall survival after mechanical circulatory support and transplantation was 0% versus 83% in the early and late periods, respectively.

ECMO has been used in seven patients as posttransplantation support (respiratory distress syndrome in three and posttransplantation lymphoproliferative disease in four); however, only the one patient noted earlier survived. A centrifugal RVAS was used for posttransplantation right ventricular support in an 18-year-old boy with tetralogy of Fallot. This young man had four prior thoracic procedures, which included a right Blalock-Taussig shunt, a Waterston shunt, a Potts shunt, and a Rastelli procedure. In addition, the patient had intraparenchymal pulmonary artery hypoplasia. The RVAS was able to be weaned and removed after 8 days. Over a period of 90 days the allograft right ventricular end-diastolic pressure declined from 20 to 8 mm Hg and the patient was discharged to his home.

Rejection. In patients who survived more than 30 days, there were 6 deaths (20%) resulting from rejection in 30 patients treated with cyclosporine (mean follow-up 1300 days) and no deaths resulting from rejection in 24 patients treated with FK 506 (mean follow-up 455 days) ($p < 0.02$, Fisher's). Two patients treated with cyclosporine-based immunosuppression required a second transplant operation (7 months and 7 years) for chronic rejection. The patient operated on at 7 months died 3 months later of persistent rejection. The patient operated on at 7

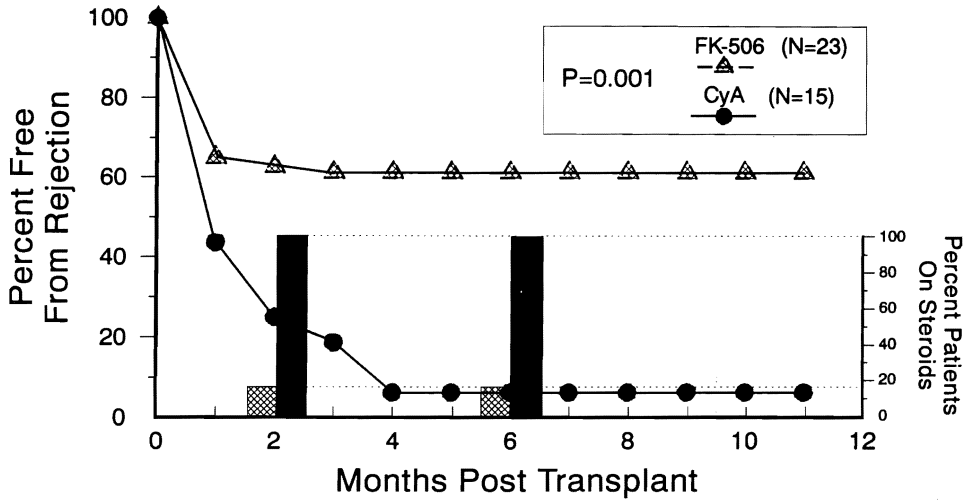

Fig. 4. Actuarial freedom from rejection in pediatric cardiac transplantation FK 506 immunosuppression compared to the cyclosporine *(CyA)* immunosuppression era.

years had persistent rejection, which was reversed with conversion to FK 506; however, she died of suicide 1½ years later.

The actuarial freedom from rejection (grade 3A or greater) in the 24 children treated with FK 506 who survived more than 30 days was 60% at 3 and 6 months after transplantation. In the 15 children undergoing transplantation before November 1989 (survival >30 days) treated with cyclosporine-based triple-drug immunosuppression and rabbit antithymocyte globulin immunoprophylaxis ($n = 5/15$), the actuarial freedoms from rejection (grade 3A or greater) were 20% and 12% at 3 and 6 months after transplantation, respectively ($p < 0.001$, Mantel-Cox and Breslow) (Fig. 4). In addition, 85% of the children treated with FK 506 were weaned off steroids, whereas all 15 patients treated with cyclosporine-based therapy continued to require steroid therapy, based on their rejection history. There were 0.9 episodes of rejection per patient in the FK 506 group; 13 of these 21 episodes occurred in 3 sensitized patients. Two patients in the FK 506 group required the addition of azathioprine and 1 patient was treated with OKT3.

Eight patients whose initial immunosuppression was cyclosporine-based therapy were switched to FK 506 for persistent grade 2, 3A, or 3B rejection. Other complications that prompted FK 506 conversion were the inability to wean steroids ($n = 8$), hypertension ($n = 6$), hyperlipidemia ($n = 4$), and graft dysfunction ($n = 1$). These "rescue" patients tolerated the switch from cyclosporine to FK 506 without significant complications. Cyclosporine was discontinued 24 to 48 hours before 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 biopsy results, steroids were tapered. Four patients were tapered off prednisone and four patients have been weaned to one quarter of their maintenance dose. All patients have either had resolution of their rejection or have significant improvement in the histologic endomyocardial biopsy grading of rejection; the one patient with graft dysfunction had restoration of normal hemodynamics. There was one death, caused by suicide, in the "rescue" group.

Infection. There were 5 (7%) deaths caused by infection in the 66 children; two of these deaths occurred in the FK 506 group. A review of infectious complications in pediatric heart transplant recipients at Children's Hospital of Pittsburgh from 1982 to 1987 has been previously reported.[7] Since November 1989, in the FK 506 study, there were 14 major infections in 10 patients. Seven (50%) major infections occurred in 2 neonates who required prolonged stays in the intensive care unit. One other patient, who required transplantation for tricuspid atresia and prior Fontan procedure, had three major infections and died of an infection. There were 15 minor infections in 10 patients. The most common (3/10) minor infection was varicella.

Cardiac function. All surviving patients have excellent cardiac function. The average left ventricular ejection fraction measured by gated nuclear scan and/or echocardiography was 66%. The range of left ventricular ejection fractions was 60% to 75% at the time of longest follow-up. The first annual coronary angiograms have

been normal in all cardiac allograft recipients treated with FK 506.

Renal function and hypertension. FK 506 was extremely well tolerated in the pediatric group of cardiac transplant recipients. The average pretransplantation serum creatinine concentration was 0.7 ng/dl (standard error 0.1) and 3 months after transplantation it was 0.9 ng/dl (standard error 0.1). Moderate oliguria and transient azotemia was associated with the intravenous administration of FK 506 particularly if preexisting renal dysfunction was present. Two patients required temporary peritoneal dialysis; one patient had renal vein thrombosis as a result of intravenous catheters and the other patient was in anuric renal failure before transplantation as a result of cardiac arrest. Normal renal function has returned in both of these patients.

Only two patients have required antihypertensive therapy. One patient who was treated for hypertension before transplantation continues to receive antihypertensive therapy. The other patient's blood pressure returned to normal after repair of an aortic coarctation. Compared with the prior cyclosporine era, in which the prevalence of hypertension was 70%, this represents a dramatic reduction in the necessity to treat hypertension in children after transplantation ($p < 0.001$, Fisher's).

Metabolic studies and side effects. No pediatric patient receiving primary or rescue FK 506 immunotherapy has required insulin therapy or had abnormal fasting blood sugar levels. Continued monitoring of hematologic and coagulation indexes, as well as of hepatic function, failed to reveal any abnormalities in our patients at this follow-up interval, with the exception of anemia. Anemia (hematocrit value <28%) has been problematic in 6 of the 24 children (survival >30 days) treated with FK 506–based immunosuppression. One of these children had a documented parvovirus infection, which caused her anemia. The other 5 children have had normal anemia studies including bone marrow biopsies. This anemia is associated with low erythropoietin levels and reticulocyte counts and has responded well to erythropoietin therapy. Further evaluation of the mechanism of this anemia is under study. Cholesterol and triglycerides have been slightly lower than those in cyclosporine-treated patients, but the difference was not statistically significant. Four patients had borderline elevation in uric acid levels. Moderately elevated serum potassium levels ($K+ > 5.5$ mEq/L) 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 cases of seizure, cerebrovascular accident, or neuropathy as a result of FK 506. One patient in the primary FK 506 therapy group had an intracerebral hemorrhage and seizure because of prior cerebral vasculitis caused by endocarditis. She recovered with minimal residual neurologic deficit. There have been occasional reports of extremity paresthesia, temperature malsensations in the hands and feet, and tremor, 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, hirsutism, or abnormalities in facial bone growth previously observed in patients treated with cyclosporine.

Posttransplantation lymphoproliferative disease. Five of 54 patients (9.2%) who survived more than 30 days have posttransplantation lymphoproliferative disease. This disease developed early (<1 year) in 3 patients, at 4, 4 and 6 months, and late (>1 year), in 2 patients, at 14 and 18 months. Four of these patients were treated with cyclosporine-based therapy, 1 of whom underwent FK 506 switch after 3 episodes of treated rejection. One patient was treated primarily with FK 506 immunosuppression. Three patients had associated infections at the time of presentation with disseminated posttransplantation lymphoproliferative disease, and they died. Two patients had localized disease in the form of multiple pulmonary nodules and responded favorably to reduction in immunotherapy. Four of these 5 (80%) patients had an Ebstein-Barr infection associated with the development of posttransplantation lymphoproliferative disease. In our previously reported experience during 10 years of cyclosporine-based immunosuppression in heart and lung transplantation, 14 of 486 (2.8%) adult cardiac recipients who survived more than 30 days had posttransplantation lymphoproliferative disease. Thus children with a cardiac allograft are at significantly greater risk for the development of posttransplantation lymphoproliferative disease ($p < 0.02$, χ^2) than their adult counterparts. The mortality from posttransplantation lymphoproliferative disease in both groups, however, was approximately 60%.

Discussion

Our early experience in pediatric heart transplantation was sobering. This was due to an exceedingly high perioperative mortality (60%) in children with congenital heart disease and a high late mortality (66%) in children with cardiomyopathy, primarily caused by rejection. In addition, children who required ECMO for pretransplantation support also had an extremely high perioperative mortality (66%). Since July 1988, 34 children have undergone heart transplantation, and the data from this more recent series are encouraging. In the 11 patients

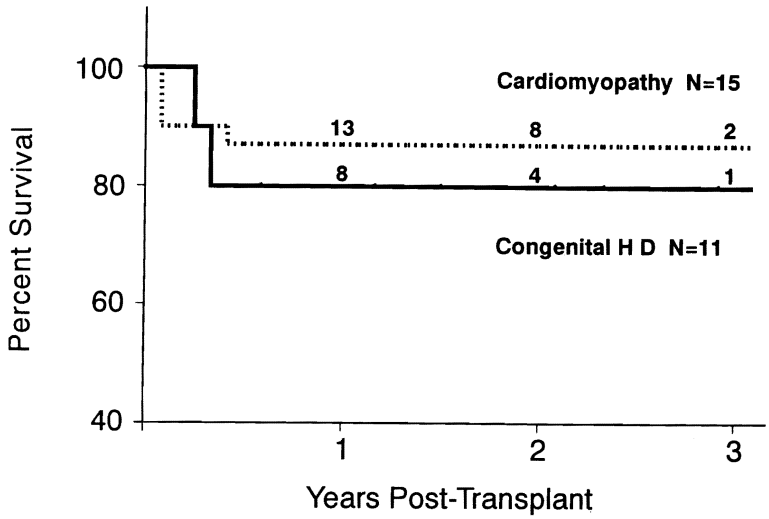

Fig. 5. Survival in pediatric heart transplantation cardiomyopathy and congenital heart disease *(HD)*. Confidence interval is not calculable.

with congenital heart disease undergoing transplantation since July 1988, the perioperative mortality was 0%. We attribute the marked improvement in perioperative survival in our patients with congenital heart disease to improved myocardial protection, surgical experience, and aggressive posttransplantation care. The difference in late mortality, 66% versus 7%, in the groups with early and late cardiomyopathy, respectively, was due to a significant reduction in mortality from rejection. Reduced mortality from rejection ($p < 0.02$) and an increased freedom from rejection ($p < 0.001$) have occurred due, in part, to our increased experience with immunosuppression and in the diagnosis and treatment of rejection, as well as to the advent of FK 506, which has a substantial immune advantage in the child.

Our experience with mechanical circulatory support in the child has also improved substantially since mid-1988. ECMO and Novacor LVAS have successfully bridged six children to transplantation. The perioperative survival in these 6 patients was 83%. Despite this encouraging trend in survival after cardiac transplantation in patients requiring pretransplantation mechanical circulatory support, a glaring deficiency in the armamentarium of the pediatric cardiac transplant surgeon is an efficient miniaturized ventricular assist device. Ideally, in the near future, this type of technology will be available and will further improve our ability to support children for safer and longer periods.

Two patients are worth special note with regard to their pretransplantation disease. One patient underwent successful heart transplantation for a cardiac angiosarcoma. This child unfortunately had epicardial spread of his tumor at the time of the operation and died 10 months after transplantation. A recently published report on cardiac angiosarcoma[8] failed to consider the potential of heart transplantation as a treatment for this rare but lethal disorder. We believe that aggressive application of cardiectomy and transplantation, coupled with chemotherapy, could potentially produce results similar to treatments for other sarcomas. The other pretransplantation disease which represents an increasing pool of pediatric heart transplantation candidates is the "end-stage" Fontan. Infection, however, was the cause of mortality in 1 of 2 Fontan patients in our series and produced substantial morbidity in the other. These patients have chronic venous hypertension and frequently have protein-losing enteropathies, hypoalbuminemia, diminished cellular and humoral immunity, malnutrition, and pleural, pericardial, and peritoneal effusions. Their posttransplantation care will, of necessity, require reduced immunosuppression and aggressive diagnosis and treatment of infection.

The trial of FK 506 immunosuppression in the adult cardiac transplant recipients has been successful.[9] However, the salutary effects of this potent immunosuppressive macrolide are far more dramatic in children. FK 506 has become essentially the only immunosuppressive agent required for children after heart transplantation. It has obviated the need for steroids, nonspecific bone marrow suppressants, and antilymphocyte agents in the majority of pediatric recipients. Posttransplantation hypertension necessitating antihypertensive treatment has been virtually eliminated ($p < 0.001$). Renal toxicity in children treated with FK 506 has been mild. The tremendously

debilitating side effects for children of hirsutism, gingival hyperplasia, and abnormal facial bone growth observed with cyclosporine have not been seen in patients treated with FK 506. Not only can children with cardiac allografts now compete favorably with their peers in terms of activity, but their outward appearance will no longer betray their difference inside. The ability of FK 506 to treat rejection and permit steroid withdrawal in patients unresponsive to conventional treatment is further testament to the potency and selectivity of this new agent.

Our more recent experience in pediatric heart transplantation would thus suggest that children with cardiomyopathy and congenital heart disease can anticipate 80% to 90% survival at the first year after transplantation (Fig. 5). In addition, high-risk children and those with cardiomyopathy of unusual cause can also benefit from the procedure, albeit at increased risk. Antenatal diagnosis of cardiac anomalies brings the fetus, as well, to the care of the pediatric cardiac transplant surgeon and challenges all of us to ensure ethical and equitable distribution of pediatric hearts for children.

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Discussion

Dr. Florentino Vargas *(Buenos Aires, Argentina).* I would like to share our initial experience at Italian Hospital of Buenos Aires with pediatric heart transplantation. We started our pediatric experience 2 years ago, after a 3-year period of preparation of the group and in the face of considerable environmental and logistic difficulties.

Since May 1990 nine children have undergone heart transplantation, the smallest one weighing 5 kg. Because of the scarcity of donors in Argentina, we accepted a considerable degree of donor-recipient mismatch in weight. In one extreme case the mismatch was 500%. In three recipients we accepted pulmonary vascular resistances higher than 5 units/m^2. Crystalloid myocardial protection was used at the donor's hospital and a dose of blood cardioplegic solution was added at our hospital in cases of distant procurement.

There has been neither hospital nor long-term mortality so far for the group. The average hospital stay was 20 days and the average follow-up, 16 months. Rejection surveillance was done by noninvasive means. Three rejections occurred during the hospital stay and the remaining within the first year. All patients are doing well, in functional class I, and have returned to their normal activities. Patients of school age resumed unrestricted school activities, and two have returned to their own environment to help their families with farm work. The latter is an aspect that must be taken into account when planning the follow-up, because our transplant recipients cannot be removed from the reality of Argentinean life.

Ours is a triple-drug protocol, and we try to use the lowest dosage we can after the first year. In our series the percentage of hypertensive, cyclosporine-treated patients was similar to the percentage that you have described. Their hypertension seems to be well controlled with vasodilators. However, continuous Holter pressure monitoring disclosed that 60% of them became significantly hypertensive at night while sleeping.

Although this phenomena has been reported after transplantation in adults, we have no references in pediatric heart transplant recipients. We managed this hypertension by rescheduling the time when the patients received the vasodilators each day. Have you noted this problem in your cyclosporine-treated patients and have you any comment about it?

Dr. Leonard L. Bailey *(Loma Linda, Calif.).* The report represents a maturation in the Pittsburgh pediatric heart transplant program. A host of variables, including surgical experience, improved technology, patient selection, and posttransplantation immunomodulation have combined to produce the markedly improved early and intermediate survival of infants and children undergoing transplantation at Children's Hospital of Pittsburgh.

The authors describe a number of potential advantages to the use of FK 506 as compared with their previous experience using cyclosporine-based triple-drug therapy. With so many variables affecting transplantation outcome in the more recent experience, I found it difficult to be sure how much of the improvement was due to FK 506 and how much was due to all these other factors. To really discover the potential advantages of FK 506, the authors, I believe, must conduct a prospective randomized study that would help eliminate many of these other variables. Perhaps a more valid measure of the benefits of FK 506 would be to compare recent Pittsburgh outcomes with those of another center with comparable outcomes in which a different immunosuppressive regimen was used. For instance, combined early and late mortality from rejection in the cyclosporine-treated group of infants in the Loma Linda University series was 6%, slightly less than the late rejection mortality of 7% attributed to the FK 506 group that you presented.

Another shortfall amid the fundamentally good news in this report from Pittsburgh is the fact that no statistical comparison was made between the cyclosporine and FK 506 groups with regard to early and late renal function. You showed us only how it turned out for the FK 506 group. It would be nice to have a comparison of the two groups on that issue too, since it *is* an issue. In addition, the assertion that FK 506 is steroid-sparing maintenance therapy is more a matter of opinion, at present, than a clearly defined fact. Our experience and that of the Harefield group suggest that chronic steroid use is not essential in cyclosporine-treated patients.

I have two questions for you. First, are you involved in a prospective randomized trial of FK 506 at Pittsburgh? If not, why not? Second, have you observed an increase in infectious complications among those patients treated with FK 506? I ask this because of our experience of an increased prevalence of lethal infections among juvenile primate recipients receiving FK 506 in the laboratory. We are all eager to have an alternative semiselective immunosuppressant available for managing infants and children, and FK 506 is an exciting prospect. It remains to be seen if it is truly an improved agent, however.

Dr. Griffith. First of all, Dr. Vargas, the benefits of the Graham Traveling Fellowship have been quite obvious with your emerging, excellent series. Early on in the cyclosporine experience there were a number of publications from many centers, ours included, suggesting that hypertension was related to postural changes and loss of reflex control.

Dr. Bailey, I appreciate your critical review of our manuscript, to date the intent of our program's use of FK 506 was not as a comparison to cyclosporine. To randomize FK 506 in children at Pittsburgh would span a decade during which the first treated patients clearly would not be representative of later recipients. I would like to see FK 506 introduced to other centers so that a more global representation of what it can do would be possible. At present the drug has been randomized in our adult lung population, which is at least a step in the right direction.

We have no explanation for your cyclosporine rejection rate being less than ours. Perhaps you have a younger group of patients or render less tissue for examination. We believe that FK 506, as has been shown in our adult population in hearts, has resulted in fewer episodes of treated rejection. Other advantages include reduced hypertension and a lack of facial brutalization.