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Clinical Trial of FK 506 Immunosuppression in Adult Cardiac Transplantation

John M. Armitage, MD, Robert L. Kormos, MD, Shigeki Morita, MD, John Fung, MD, Gary C. Marrone, MD, Robert L. Hardesty, MD, Bartley P. Griffith, MD, and Thomas E. Starzl, MD, PhD

Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

The new immunosuppressive agent FK 506 was used as primary immunotherapy in conjunction with low-dose steroids and azathioprine in 72 patients subsequent to orthotopic cardiac transplantation. Overall patient survival at a mean follow-up of 360 days was 92%. The number of episodes of cardiac rejection (grade 3A or greater) within 90 days of transplantation was 0.95 per patient. The actuarial freedom from rejection at 90 days was 41%. Achievement of this level of immunosuppression is comparable with that of cyclosporine-based triple-drug therapy with OKT3 immunoprophylaxis. Thirty percent of patients were tapered off all steroids, and the average steroid dose in the group who received steroids was 8.6 mg of prednisone per day. The incidence of infection reflected the diminished necessity for steroids: seven major infections (10%) and 11 minor infections (16%). Renal dysfunction occurred during the perioperative period in most patients in this trial. However, the incidence of hypertension was 54% compared with 70% during the cyclosporine era. Ten adults underwent successful rescue therapy with FK 506 after cardiac rejection refractory to conventional immunotherapy. Side effects of FK 506 were notably few, and the results of the trial are encouraging for the future of the cardiac transplant recipient.

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The potent immunosuppressive macrolide antibiotic FK 506 has undergone clinical testing at Presbyterian-University Hospital since January 1989. The initial clinical trials were designed for liver transplant recipients with refractory rejection [1, 2], and pursuant to the dramatic and gratifying results, FK 506 was introduced as the basis of immunosuppression in kidney and liver transplant recipients in March 1989 [3, 4]. Since October 1989, in a prospective clinical trial, 72 patients have undergone orthotopic cardiac transplantation using primarily FK 506 and low-dose steroids as immunosuppression. Dramatic results were also attained in 10 patients with cardiac rejection refractory to all known conventional treatment who underwent rescue therapy with FK 506.

Material and Methods

Primary Patient Group

Seventy-two patients were prospectively entered into this study from October 1989 to January 1992. Informed consent was obtained from each patient before transplantation for the use of FK 506 and steroids as the foundation of immunosuppressive therapy; 10 patients received conventional cyclosporine-based immunosuppression during this period. These 10 patients either had hemorrhage or hemodynamic problems that precluded the initiation of FK 506 therapy within 24 hours of transplantation or refused consent. No attempt was made to selectively enroll patients in this study based on severity of illness, preoperative United Network for Organ Sharing status, or preoperative end-organ function.

In the study group, there were 59 men and 13 women ranging in age from 24 to 61 years. Eight patients (11%) required mechanical circulatory support before transplantation in the form of the Novacor left ventricular assist device (6), the Thoratec left ventricular assist device (1), and a total artificial heart (1). Six other patients awaited transplantation with intraaortic balloon pump support. The cause of cardiomyopathy included ischemic (32), idiopathic (23), valvular (6), myocarditis (4), hypertrophic (3), retransplantation (3), and congenital heart disease (1). Panel reactive antibody was less than 10% in all but 3 patients. Mean follow-up was 360 days (range, 5 to 827 days) as of January 1992.

Rescue Patient Group

The criteria for the use of FK 506 as a "rescue" agent were strictly dependent on persistent grade 3A rejection and previous treatment with triple-drug therapy (cyclosporine, azathioprine, and steroids) and conventional rescue therapy for rejection of at least two courses of intravenous steroids and one or more courses of antilymphocyte therapy (antithymocyte globulin, antilymphocyte globulin, or OKT3).

The 10 patients in the rescue group represented an extremely heterogeneous population. Six of them were referred to our institution from other centers. They were younger (age range, 22 to 50 years) and were seen earlier after transplantation (range, 3 to 22 months; average, 8

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Address reprint requests to Dr Armitage, Department of Surgery, University of Pittsburgh, 1084 Scaife Hall, Pittsburgh, PA 15261.

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months) than those from our own center. All 6 patients referred for FK 506 rescue had refractory grade 3A or greater rejection and had received at least one course of OKT3 and two courses of intravenous methylprednisolone. Three of the 6 had received both antithymocyte globulin and OKT3. One patient had had two courses of antithymocyte globulin and one course of OKT3. Another patient had had a course of methotrexate. All of these patients were receiving high-dose cyclosporine, azathioprine, and prednisone, 20 to 50 mg/day. One patient had had a panel reactive antibody of 60% before transplantation, had acutely rejected the first transplanted heart, and was supported on extracorporeal membrane oxygenation for a week before retransplantation. She then had persistent rejection of the second heart and was referred for rescue.

The 4 patients from our center (age range, 53 to 67 years) had undergone transplantation 1 year to 4 years previously (average time, 2.5 years). All had received one to two courses of antithymocyte globulin and one to two attempts at steroid therapy and had persistent grade 3A rejection.

FK 506 Therapy

FK 506 treatment was begun as an intravenous loading dose within 6 to 12 hours after transplantation. In the early clinical trial, from October 1989 to August 1990, 23 patients received 0.15 mg · kg^{-1} · day^{-1} of FK 506 in two divided doses, each over 4 hours, for a duration of 24 to 72 hours. As soon as gastrointestinal function returned, oral FK 506 was initiated at a dose of 0.3 mg · kg^{-1} · day^{-1}, with the first oral dose given with the last intravenous dose. Since August 1990, 49 patients have received 0.05 mg · kg^{-1} · day^{-1} of FK 506 as a continuous intravenous infusion as a loading dose begun within 6 to 12 hours after transplantation for 24 to 48 hours. Oral administration of FK 506 was begun at 0.3 mg · kg^{-1} · day^{-1} after the intravenous infusion was completed. The oral dose of FK 506 was targeted for a serum level of 0.7 to 1.5 ng/mL (12-hour trough enzyme-linked immunosorbent assay by the technique of Tamura and colleagues [5]) depending on renal function and rejection history. The oral maintenance dose to attain target levels ranged from 0.04 to 0.4 mg · kg^{-1} · day^{-1} with an average oral dose of 0.15 mg · kg^{-1} · day^{-1}.

Steroid Therapy

Methylprednisolone, 7 to 10 mg/kg, was administered intravenously in the operating room and in three divided doses for a total of 5 mg/kg in the first 24 hours after transplantation. Thereafter, patients received oral prednisone, 0.15 mg · kg^{-1} · day^{-1}. In the early trial (October 1989 to August 1990), steroid weaning was begun at the first week after transplantation based on freedom from rejection. Since August 1990, steroid weaning has begun at the 12th posttransplant week, again based on freedom from rejection.

Other Agents

Azathioprine was reserved as an adjunctive immunosuppressive agent to aid in control of rejection or to allow lower FK 506 treatment in patients with renal dysfunction. OKT3 was reserved for severe rejection associated with hypotension or hemodynamic compromise.

All patients entered into the FK 506 immunotherapy protocol were placed on a regimen of prophylactic oral trimethoprim/sulfamethoxazole and nystatin (Mycostatin; E.R. Squibb & Sons, Princeton, NJ). Acyclovir was administered for the first 6 months after transplantation and discontinued thereafter.

FK 506 Rescue Therapy

"Rescue" treatment required a 7- to 14-day hospitalization. The medical records and endomyocardial biopsy slides of the patients were reviewed, and complete blood screening as well as chest and abdominal computed tomographic scans were performed. Cyclosporine administration was discontinued the day of admission, and in 8 of the 10 patients, azathioprine was also discontinued. Steroid dose was diminished to half the maintenance dose. No intravenous loading dose of FK 506 was administered. The patients were begun on a regimen of oral FK 506, 0.3 mg · kg^{-1} · day^{-1}, in two divided doses, and FK 506 levels were targeted at 1 to 1.5 ng/mL. Cardiac function was evaluated by multigated acquisition scan and echocardiography before and after FK 506 rescue. An endomyocardial biopsy was performed on day 7. If rejection had resolved by day 7, the patient was discharged and followed with endomyocardial biopsy, echocardiography, blood work, and measurement of FK 506 levels. If rejection had not resolved at the time of the first biopsy, the patient had a second biopsy on day 14. All rescue patients were discharged home within 14 days.

Monitoring for Rejection

Surveillance of all patients after transplantation involved weekly transvenous endomyocardial biopsies during hospitalization and at slowly increased intervals after discharge. Biopsy specimens 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 the standardized nomenclature for cardiac rejection [6]. Biopsy specimens that were read before the advent of the standardized nomenclature were retrospectively reviewed and graded according to the new standardized method.

Monitoring for Infection

All patients were followed up by a specialist in infectious disease. Titers for hepatitis B virus, herpesvirus, Epstein-Barr virus, human immunodeficiency virus, *Toxoplasma*, and cytomegalovirus were performed on all donors and recipients before transplantation. The diagnosis of infection was made using clinical criteria as previously defined by this institution [7]. 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 throughout follow-up.

Results

Survival

Sixty-six (92%) of the 72 patients entered into this trial are alive. The perioperative mortality (30 days after transplantation) was 4%. The causes of the 3 early deaths were as follows: secondary to pulmonary hypertension/right heart failure; disseminated aspergillosis; and unknown. The patient with an unknown cause died suddenly on an exercise cycle at home; he had had no episodes of rejection at four biopsies; permission for postmortem examination was denied.

The late mortality (>30 days after transplantation) was 4%. The first late death was secondary to low cardiac output (day 54); there was no evidence of rejection, cellular or humoral, or serious coronary artery disease at postmortem examination. The second late death was due to pneumonia, empyema, and colitis (month 6), and the third, to myocardial infarction and coronary arteriopathy after gratting (month 10). No death has been attributed to FK 506 therapy or to acute or refractory cardiac rejection.

Rejection

Rejection was defined as any histological diagnosis of grade 3A or greater. An episode of rejection was defined as one biopsy grade of 3A or greater, irrespective of sequential occurrence. Recurrent rejection was defined as a biopsy grade of 3A or greater after treatment and resolution of a prior episode of rejection.

In the primary therapy group there were 72 patients, 67 of whom were followed up for 90 days or more. We analyzed this group as a whole and also as two groups based on the FK 506 intravenous induction dose: group 1, 0.15 $mg \cdot kg^{-1} \cdot day^{-1}$ (n = 20), and group 2, 0.05 $mg \cdot kg^{-1} \cdot day^{-1}$ (n = 47).

Of these 67 patients, 33% never had an episode of rejection, and 67% had at least one episode. The mean number of days to the first episode of rejection was 37 ± 52 (median, 16 days; range, 6 to 237 days). The mean number of episodes of rejection per patient within 90 days was 0.95 ± 1.01 (median number, 1). Recurrent rejection occurred in 27.6% of the total group. The actuarial freedom from rejection at 90 days was 41% and at 180 days, 34% (Table 1).

The high-dose (0.15 $mg \cdot kg^{-1} \cdot day^{-1}$) FK 506 induction group (group 1) was analyzed and compared with the low-dose (0.05 $mg \cdot kg^{-1} \cdot day^{-1}$) group (group 2). The actuarial freedom from rejection at 90 days was 40% versus 41%, respectively. Statistical analysis failed to reveal any significant difference between the two groups in the variables of rejection studied with the exception of the mean number of days to the first episode of rejection (Table 2).

Table 1. FK 506 Versus OKT3/Triple-Drug Immunosuppression

Variable	OKT3/Triple Drug (n = 43)	FK 506 (n = 67)
Mean time to first grade 3 rejection (d)	33 ± 5.6	37 ± 52
Percent rejection free at 90 days	40	41
Rejection episodes/patients at 90 days	1	0.95
Percentage with recurrent rejection	48	28[a]

[a] Significance: $p < 0.01$ by χ^2 analysis.

Table 2. Low-Dose Versus High-Dose FK 506 Immunosuppression[a]

Variable	Group 1 (n = 20)	Group 2 (n = 47)
Mean time to first grade 3 rejection (d)	34	14[b]
Percent rejection free at 90 days	40	41
Rejection episodes/patients at 90 days	0.95	0.95
Percentage with recurrent rejection	20	31

[a] Group 1 received 0.15 $mg \cdot kg^{-1} \cdot day^{-1}$ and group 2, 0.05 $mg \cdot kg^{-1} \cdot day^{-1}$. [b] Significance: $p < 0.01$.

Twenty-one (31%) of the 67 patients had FK 506 as the only immunosuppressive agent. Thirty-nine (58%) were given prednisone (5 to 10 mg/day), and 28 (42%) required azathioprine. Twenty-one patients (31%) were on a regimen of triple therapy (FK 506, azathioprine, and prednisone). Only 3 patients (4%) required OKT3 for severe rejection.

Seven of the 10 patients in the rescue group were free from rejection after the FK 506 switch. The other 3 each required one subsequent treatment to resolve rejection: 1 received a prednisone taper; 1, an intravenous dose of methylprednisolone for 3 days; and 1, intravenous methylprednisolone and OKT3. The average length of follow-up in this group was 11 months. The average maintenance dose of FK 506 in the rescue group was 0.12 $mg \cdot kg^{-1} \cdot day^{-1}$. Eight of the 10 patients remained on a regimen of steroids but at considerably lower doses; the average prednisone dose was 20 mg/day before rescue and 7.5 mg/day after rescue. Four patients were treated with azathioprine and FK 506, 3 of whom were also receiving prednisone.

Infection

Four major infections were present in 3 patients before cardiac transplantation. One patient had two infections before transplantation: staphylococcal line sepsis secondary to an intraaortic balloon pump and sternal *Candida* osteomyelitis at the time of removal of a Novacor left ventricular assist device. This same patient had pulmonary emboli and infarctions before placement of the device but remained free from infection after transplantation with FK 506 as the sole immunosuppressive agent. Amphotericin was administered for 5 weeks after transplantation, and the patient recovered without sequelae. The second patient had a *Klebsiella* pneumonia during intraaortic balloon pump support, received 8 days of antibiotic therapy before transplantation, and recovered without further infection. The third patient with an infection before transplantation had endocarditis and line sepsis with sterile blood cultures before transplantation. He also recovered without complications.

After transplantation, there were 18 infections in the 67 patients followed up for 90 days or more. There were seven major infections (10%) in 5 patients, with two deaths secondary to infection; one was due to disseminated aspergillosis and one, to a gram-negative pneumonia/empyema with subsequent *Clostridium difficile* colitis. One patient had a pulmonary abscess and subsequently had development of an aortic suture line mycotic aneurysm, which was diagnosed by magnetic resonance imaging and repaired. Another patient had two pneumonias, pneumococcal and pneumocystic. The seventh major infection was a *Proteus* and staphylococcal abdominal wound infection after explantation of a Novacor left ventricular assist device. There were 11 (16%) minor infections, six of which were gastrointestinal cytomegalovirus.

In the rescue group, 5 (50%) of the 10 patients had infections before or at the time of the FK 506 switch. Two patients had cytomegalovirus and herpetic infections, 3 had cytomegalovirus alone, and 1 patient had a ruptured aortic suture line *Salmonella* mycotic aneurysm. Subsequent to FK 506 rescue, there were three infections: bronchitis, gastritis, and pneumonia.

Cardiac Function and Coronary Arteriopathy

All surviving patients had excellent cardiac function. In the primary patient group, the average left ventricular ejection fraction measured by gated nuclear scan, echocardiography, or both was 0.66. The range was 0.48 to 0.75 at the time of longest follow-up. The average left ventricular ejection fraction in the rescue group was 0.61 (range, 0.47 to 0.70) before the switch and 0.63 (range, 0.50 to 0.76) after rescue.

Coronary arteriopathy after transplantation was defined as any luminal irregularity or any degree of coronary stenosis. To maximize the possibility of detecting coronary disease transplanted from the donor to the recipient, any recipient of a donor heart 40 years or older had coronary angiography before discharge after the transplant procedure. There were 4 such patients, and all the coronary studies were normal. The average donor age was 35 years (range, 19 to 49 years). At the 1-year-follow-up interval, 35 patients have undergone routine left and right heart catheterization with coronary angiography, and 4 patients (11%) have had posttransplantation coronary arteriopathy. There was one death due to myocardial infarction in a patient with detected coronary disease at 1 year.

Renal Function and Hypertension

In the 67 patients followed up for 90 days or more, the mean creatinine level before transplantation was 1.3 ng/dL (± 0.8) and at 3 and 6 months after transplantation, 1.9 ng/dL (± 0.7) and 2.2 ng/dL (± 0.5), respectively. In group 1, with high-dose intravenous induction, the mean pretransplantation creatinine level was 1.4 ng/dL and at 3 and 6 months after transplantation, 2.3 ng/dL. In group 2, with lower dose intravenous FK 506 induction, the mean pretransplantation creatinine level was 1.3 ng/dL and at 3 and 6 months after the procedure, 1.8 ng/dL and 2.1 ng/dL, respectively. Although there was no significant difference in serum creatinine level between the two groups, 4 patients required dialysis in the perioperative period, 3 of whom were in group 1. Peak renal dysfunction occurred at the first postoperative week with an average serum creatinine level of 2.3 ng/dL (± 1.03). In the rescue group, the switch to FK 506 was very well tolerated with respect to renal dysfunction. The average serum creatinine level was 1.3 ng/dL before rescue and 1.8 ng/dL after rescue.

Thirty-six (54%) of the 67 patients had diastolic hypertension necessitating antihypertensive therapy. All 36 patients were treated with a single agent, either enalapril maleate or diltiazem hydrochloride. In the rescue group, 7 of the 10 patients had hypertension before rescue, and all 7 continued to require treatment while receiving FK 506. However, 2 of the 7 patients were able to control the hypertension with single-drug as opposed to double-drug therapy on a regimen of cyclosporine.

Metabolic Studies and Side Effects

There were 20 insulin-dependent diabetics among the 67 patients receiving primary FK 506 therapy after cardiac transplantation. Four of the 20 were insulin dependent before transplantation (2 had juvenile-onset diabetes mellitus), and 3 were non–insulin-dependent diabetics. There were 12 new-onset insulin-dependent diabetic patients (20%) among 60 nondiabetic recipients. Ten of the 12 with new-onset diabetes were also on a regimen of prednisone (average dose, 7 mg/day).

Continued monitoring of hematological and coagulation indices as well as hepatic function failed to reveal any abnormalities at this follow-up interval. Cholesterol and triglyceride levels have been slightly lower than those in cyclosporine-treated patients, but not significantly so. Five patients have borderline elevated uric acid levels. Elevated serum potassium levels ($K^+ > 5.0$ mEq/L), which required treatment with furosemide, were seen in 8 patients. This abnormality in K^+ excretion was independent of renal function and has been observed in other organ recipients treated with FK 506.

Side effects have been rare despite routine questionnaires during hospitalization and during outpatient follow-up. There have been no seizures, cerebrovascular accidents, or neuropathies secondary to FK 506. One patient in the primary therapy group had a thromboembolic occipital cerebrovascular accident 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 experienced akinetic mutism while receiving FK 506, which led to a reduction in the dose. He has since recovered and returned to work. Muscle aches, mild insomnia, and tremor were also reported. Notably absent in this patient group were complaints of gingival hyperplasia or hirsutism.

Posttransplantation Lymphoproliferative Disease

Ten months after transplantation, 1 patient (1.4%) in the primary therapy group had development of an inflammatory cervical adenopathy, which on excision biopsy was consistent with posttransplantation lymphoproliferative disease. Reduction in immunotherapy resulted in resolution of the process, and no recurrence has been detected at 16 months' follow-up. Two months after rescue, 1 patient in the rescue group also had posttransplantation lymphoproliferative disease, which manifested as gastrointestinal hemorrhage necessitating laparotomy. Again, reduction in immunotherapy led to resolution of the disease process. Her immunosuppression regimen before rescue had consisted of four courses of intravenous steroids and OKT3 with cyclosporine, azathioprine, and prednisone over a 2-month period.

Comment

These early results with FK 506 as the basis of immunosuppression hold tremendous promise for the future, both as primary immunotherapy in cardiac transplantation and as an effective agent for rescue therapy in refractory cardiac rejection. In a prospective, randomized study [8] performed at the University of Pittsburgh comparing rabbit antithymocyte globulin with OKT3 immunoprophylaxis plus cyclosporine-based triple-drug therapy, the OKT3 immunoprophylaxis group had an actuarial freedom from rejection at 90 days after transplantation of 40% with 1.0 episode of rejection per patient. The actuarial freedom from rejection in the FK 506 and low-dose steroid immunotherapy group at 90 days after transplantation in our study was 41% with 0.95 episodes of rejection per patient. However, the percentage of recurrent rejection was 48% with OKT3/cyclosporine versus 28% with FK 506 ($p < 0.01$, χ^2 analysis).

We have been impressed with the ability of this new agent to attain immunosuppression in cardiac transplant recipients comparable with 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, and with marked reduction in steroid and azathioprine requirements. Twenty-eight (42%) of the 67 patients in this study who were followed for 90 days or more receive no steroids at all. The average steroid dose for those adults on a regimen of prednisone is 8.6 mg/day. The dramatic ability of FK 506 to reverse cardiac rejection that has been refractory to aggressive treatment with conventional immunotherapeutic tools and the relatively low rate of major (10%) and minor (16%) infections are further testament to the potency and selectivity of its immunosuppressive actions.

Another advantage of FK 506 is the flexibility it introduces to immunosuppressive management. Mild to moderate rejection (grades 1A, 1B, and 2) was treated preferentially 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 biological and immunologic basis for this quality of FK 506 is presently under intense study at the University of Pittsburgh. Despite the immunosuppressive potency of FK 506, the incidence of early posttransplantation lymphoproliferative disease (1.4%) in the cardiac recipient is similar to the incidence (1.8%) observed in the previous decade of cyclosporine-based immunotherapy [9].

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 occurred in patients receiving FK 506 intravenously in the perioperative period in our attempt to achieve high early FK 506 levels (group 1). We have changed initial bolus intravenous FK 506 therapy to continuous infusion and have lowered the initial intravenous dose to a single 24-hour constant infusion dose at 0.05 mg/kg, with enteral FK 506 begun on the first postoperative day (group 2). Attendant with reduction of the postoperative intravenous loading dose of FK 506, the median time to first grade 3A rejection was diminished from 34 to 14 days.

We believe that the intravenous induction dose is important to gain appropriate early downregulation of the immune system. Further refinements in our knowledge regarding FK 506 dosage and therapeutic levels, together with the diminished incidence of hypertension, may actually improve the long-term outlook for renal function in cardiac transplant recipients. The incidence of hypertension was 54% in the FK 506 group versus 70% in the 40 cardiac transplant recipients at the University of Pittsburgh before October 1989.

FK 506 does have a negative effect on the beta islet cell, and this is reflected in the 18% incidence of new-onset diabetes in the adult population. This diabetogenic effect was enhanced by the necessity for steroid therapy in 10 of these 13 patients.

As cyclosporine had little impact on the manifestation of chronic allograft rejection or coronary arteriopathy, the full impact of FK 506 has yet to be determined. The 1-year incidence of coronary arteriopathy was 11%. Until we improve our understanding of the mechanisms and immunobiology of this process and are able to target different arms of immune upregulation, posttransplantation coronary arteriopathy will continue to occur at a predictable rate and threaten the long-term survival of the cardiac transplant recipient.

Cardiac function and the quality of life [10] in our patient group have been excellent. Concerns regarding vasculitis and neuropathy have not been realized. The diminished need for steroids, nonspecific bone marrow suppression, and antilymphocyte and antihypertensive therapy holds tremendous promise for the future of cardiac transplant recipients.

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DISCUSSION

DR R. MORTON BOLMAN III (Minneapolis, MN): The Pittsburgh group has made many contributions over the last 10 years in the field of heart transplantation and, indeed, thoracic organ replacement in general. I think this careful study of a new drug that hit with quite a splash a year or so ago is another indication of the debt that we owe these investigators. I have a couple of comments and then a couple of questions for Dr Armitage.

In 1981 when cyclosporine was introduced with similar fanfare, early results indicated that cyclosporine alone or even combined with prednisone was not an adequate regimen, and regimens using multiple therapy were developed. In 1983, we introduced the triple-therapy concept, which you alluded to with FK. We and others found that this is a much better regimen in terms of a lower incidence of rejection and infection and better overall survival. We have employed this regimen in all subsequent heart, lung, and heart-lung recipients and continue to find it effective.

In light of these results, why would you propose that we switch to FK? We now are observing approximately 80% rejection-free survival at 1 year, and others using triple therapy have had at least 50% rejection-free survival at 1 year and beyond. We have similar rates of infection, and we have never employed induction or immunoprophylaxis as you indicated you had.

Second, I think an important concept is the one you introduced for refractory rejection. This is an exciting and potentially very important area, although I am puzzled by the average ejection fraction of greater than 0.60 in your refractory rejection group. This corresponds to our experience, but nonetheless, this may be an exciting potential application for this drug.

Third, the bottom line for any of these regimens is what their impact will be on coronary artery disease. This is still the major long-term impediment to survival. Based on either investigational or clinical grounds, what are your initial impressions concerning any advantage of this agent over the regimens we use today?

DR ARMITAGE: I appreciate your comments very much. I would not encourage everyone to switch immediately to this drug. It is difficult to make an impact on the survival curves that we have nowadays, and the survival curves with this agent are similar to the very good survival curves produced by any other center using cyclosporine. No immunosuppressive agent is to be used in a cookbook fashion, and certainly with this agent there was a learning curve associated with its use.

One major advantage for some of these patients is the quality of life, mainly in terms of side effects. Hypertension, although seen, is not so difficult to treat. We have no patients on a regimen of double antihypertensive therapy, as is frequently seen with the cyclosporine group, and this may affect long-term renal function. That would be one benefit.

Hirsutism would not be so bad for myself and other gentlemen of my age group, but for a 20-year-old woman, it is a problem, and a few of our pediatric patients were switched from cyclosporine for that reason. Hirsutism has not been seen with FK 506, nor has gingival hyperplasia. Some of the side effects of the drug are less troublesome, which may have some benefit in terms of quality of life, but it is difficult to have an impact on survival when we are doing so well already. I think the attempt is to improve the quality of life, and this agent may have some benefit in that realm.

Regarding coronary artery disease, the incidence of coronary arteriopathy after transplantation in our FK group is actually a little high, although not outside the norm. One concern about the drug was that in animal studies, it was seen to cause vasculitis in large animals, and part of the reason that it was not tried in many other centers, I think, was the concern that it would produce coronary vasculitis. We have not seen that or any other systemic, muscular, or central nervous system vasculitis. I think the hope that FK 506 will diminish or preclude the event of coronary arteriopathy is a false hope, as it was for cyclosporine. One of the predictors that we have seen for the negative existence of coronary arteriopathy is treatment for rejection. Is it worthwhile giving patients a dose of steroids or pulse therapy 6 months, 9 months, and 12 months postoperatively even if they have not had an episode of rejection to try and address this issue of arteriopathy after transplantation?

Regarding the rescue group, although ejection fractions were not diminished in all of the patients, many of them had had episodes of diminished ejection fraction. Most had been able to maintain adequate ventricular function with traditional rescue agents but were unable to clear the cellular response of rejection, which was achieved with FK 506. I think that it can be an effective rescue agent, and when it is available, I think it will be another method by which to treat the problems of the solid-organ transplant recipient.

DR JOGINDER N. BHAYANA (Buffalo, NY): I enjoyed your report very much. My question concerns the rescue therapy.

Have you seen patients who had rejection with FK 506, and did you then try cyclosporine therapy as rescue therapy?

DR ARMITAGE: Only 3 patients required rescue therapy, and they were treated with OKT3 and had resolution.

DR JOEL D. COOPER (St. Louis, MO): My comments concern your creatinine levels. You reported a mean creatinine level of about 2 mg at 6 months, which I find very worrisome. How does that compare with the creatinine levels of your historic controls of a similar group of patients? Could you comment specifically on what I consider a fairly high creatinine level at 6 months postoperatively?

DR ARMITAGE: There is no question that the drug has nephrotoxicity. We have learned to ameliorate this a little by diminishing the intravenous induction dose, although that has not yet reached significance. I share your concern about the drug's nephrotoxicity. The learning curves associated with the use of the drug are very similar to those for cyclosporine, and if you look at the early experience with cyclosporine, similar rises in creatinine levels and decreases in renal function were seen. Once again, the early attempts were made to try to use the drug as a sole agent. I think perhaps that is a mistake and that it can best be used with adjuvant agents.

One thing I did not mention, mainly because this presentation was about adult patients, is that the drug has a major immune advantage in pediatric patients. Its nephrotoxicity appears to be minimal in children, and most children who had heart transplantation with FK 506 immunosuppression are free from nephrotoxicity and from the use of any other agent. I think a very exciting role for this agent is its use in both heart and lung transplantation in children.

DR COOPER: Is there a significant difference in the creatinine level at 6 months between the FK group and the cyclosporine group with which you compared it?

DR ARMITAGE: When we reviewed the cases of the 40 patients undergoing transplantation at our center before the advent of FK 506 and treated with cyclosporine, the average creatinine level in that group was about 1.7. It was about 2.1 in the FK group at 6 months. That is not a significant difference. However, from the standpoint of renal function, patients tolerate cyclosporine as we use it now better than FK 506 as used in this study.