CHAPTER 9

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INFLUENCE OF FK506 IN CLINICAL TRANSPLANTATION

John J. Fung, M.D., Ph.D.*, Ronald Shapiro, M.D.*, John Armitage, M.D.#, and Thomas E. Starzl, M.D., Ph.D.*

From the Department of Surgery, Divisions of Transplantation Surgery*, and Cardiothoracic Surgery#, at the University of Pittsburgh School of Medicine, Pittsburgh, PA and the Veterans Administration Medical Center, Pittsburgh, PA.

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Address correspondence to: John J. Fung, M.D., Ph.D.
Department of Surgery
Division of Transplant Surgery
University of Pittsburgh
3601 Fifth Avenue
Pittsburgh, PA 15213

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INTRODUCTION

With the introduction of cyclosporine A (CsA) into clinical transplantation, survival rates for patient and grafts have improved dramatically. Nevertheless, allograft rejection and the consequences of treatment of rejection continues to be the most common cause of retransplantation and death. Clinical rejection occurs in up to 80% of solid organ allograft recipients, who are maintained on ~~cyclosporine~~ CsA and steroid therapy. In addition, a number of toxicities, including nephrotoxicity may limit the optimal use of ~~cyclosporine~~ CsA. Chronic renal damage and functional impairment has been shown to occur in transplant patients, and hypertension, requiring antihypertensive therapy, occurs in the majority of these patients. Alterations in clinical immunosuppression to prevent or reverse these and other side effects have included: 1) reduction of ~~cyclosporine~~ CsA dose or 2) addition of azathoprine, antilymphocyte antibodies, or other agents with concomitant reductions in the ~~cyclosporine~~ CsA dose. These methodologies have their inherent dangers; increasing susceptibility to rejection and increased susceptibility to infection, respectively.

FK506 is a potent and novel immunosuppressive agent, discovered in Japan less than 4 years ago (1-3). A detailed summary of the preclinical development of FK506 has been published in monograph form (4-6) and in chapters 2, 7 and 8 of this volume. The purpose of this chapter is to summarize the experience of FK506 in solid organ transplantation at a single center, with appropriate notation of results of FK506 experiences, as reported in the literature.

LIVER RESCUE THERAPY

at the University of Pittsburgh Medical Center (UPMC).

A Phase I/II trial of FK506 was initiated in 1989 as the first use of FK506. The indication for FK506 therapy was in patients who were rejecting their liver allografts, in spite of conventional immunosuppression. The protocol was initially designed to combine low doses of FK506 with ~~cyclosporine~~ CsA. This combination was attempted in the first eleven patients, but was accompanied by a number of adverse reactions. Eventually, a simple switch (clean conversion) was made from ~~cyclosporine~~ CsA to FK506 (7).

All patients had an initial entry diagnosis of uncontrolled liver allograft rejection and/or other complications related to ~~cyclosporine~~ CsA, i.e. renal dysfunction or hypertension. These patients were therefore considered treatment failures of conventional immunosuppression. Prior to conversion to FK506, maintenance immunosuppression in all patients was with ~~cyclosporine~~ CsA and prednisone, with or without azathioprine. ~~Cyclosporine~~ CsA doses had been maximized to tolerable levels, as limited by renal dysfunction or hypertension.

The results of this study showed a marked ability of FK506 to reverse ongoing rejection, even in cases where chronic changes were observed (7,8). These results have subsequently been verified by a number of ~~international and American experiences~~ other centres, both in the United States and Europe (9-13). In this high risk group of patients, many ~~who have~~ of whom had received azathioprine, OKT3 and high doses of steroids, a beneficial effect of FK506 was not originally expected to be a major one. Yet, over 70% of patients treated by conversion to FK506 had both clinical and histopathologic responses. Marked improvement in biochemical parameters were noted in a majority of patients. Those patients who did not respond to FK506 conversion, had histopathologic

evidence of end stage chronic rejection, with obliteration of vascular lumen, and total disappearance of intrahepatic bile duct structures. Nevertheless, a number of patients, with marked liver function abnormalities, responded by returning to normal levels.

The United States Multi-center FK506 Liver Study Group recently analyzed the prognostic factors for successful conversion from ~~cyclosporine~~ CsA- to FK506-based immunosuppressive therapy for refractory rejection (Fujisawa Pharmaceutical Co., Ltd., personal communication). A total of 125 patients were studied. The median time to FK506 conversion from transplantation was 143 days (range 13 to 3269 days). ~~78~~ Seventy three patients were treated for refractory acute rejection, 44 for chronic rejection and 6 for both. Two patients had unknown causes for liver allograft dysfunction. At one month after conversion, 54% of patients were noted to have had complete or partial response or to have clinically improved. By 6 months after conversion, this benefit was noted in 67% of patients, and 86% at one year. The one year actuarial graft and patient survival after FK506 conversion was 50% and 72%, respectively. Multivariate analysis of risk factors showed that the following were adversely related to graft survival: elevated total bilirubin and serum transaminases, as well as previous liver transplantation. Patients with a total serum bilirubin of 13 mg/dl had a 5.1 time greater risk of graft failure and 3.1 time greater risk of death as compared to those with a serum bilirubin of 2 mg/dl or lower. Similarly, those with a baseline SGOT of 300 IU/L had a 2.5 time greater risk of graft failure than those with a SGOT of 80 IU/L or lower, but were not at a higher risk of dying. The mean Kornofsky score was 58 pre-conversion and 85 at 6 and 12 months after FK506 conversion.

PRIMARY LIVER TRANSPLANTATION

An initial primary treatment study was begun in August 1989, at the UPMC. These patients were the first human subjects to be given FK506, along with low dose steroids, as their primary immunosuppressive baseline regimen (14). FK506 was shown to be remarkably potent and successful as primary immunosuppression in liver transplantation. In the initial series of patients, a total of 92 (92.7%) of the 110 FK506 primarily treated liver transplant patients were alive between 6 and 12 months (15). These results were statistically better than those of the 325 patients in the CsA-treated control group. The rate of retransplantation was over one half less than the retransplant rate seen in the CsA control group. In these studies, 3 broad areas of toxicity were noted: nephrotoxicity, neurotoxicity, and alterations in carbohydrate metabolism.

Our initial impression was that FK506 was as effective as CsA, although the overall risk/benefit ratio required further study. A randomized trial was performed to compare FK506 with CsA (16,17). The design of this study was to use FK506 and CsA, along with steroids, in a randomized fashion, in patients undergoing primary liver transplantation. The primary endpoint was the failure of the defined treatment to prevent and control rejection. Our presumption was that graft and patient survival would be essentially the same between the two treatment groups because patient outcome after treatment failure would be individualized to each patient as deemed necessary by the investigator. Therefore patient and graft survival was considered only as a secondary endpoint. The rejection free rates was chosen as the primary endpoint in order to provide sufficient objective

evidence to resolve the key question of efficacy of either FK506 or ~~cyclosporine~~ CsA.

Two sequential phases of the randomized trial were constructed. ~~CyA~~ CsA and FK506 were given in the same manner in both phases, the only differences being the steroid dosing for the ~~cyclosporine~~ CsA arm. In "Phase 1", a rejection episode was treated with a single bolus of one gram of methylprednisolone. In "Phase 2", augmented steroid therapy was given to the ~~cyclosporine~~ CsA arm in attempts to normalize the ~~cyclosporine~~ CsA therapy with other multicenter protocols. In both phases, if this treatment failed to reverse the rejection episode, then further treatment was individualized. In both phases, the FK506 arm was kept on the same doses of steroids. Thus the FK506 arm with low dose steroids (LDS) was compared to two different ~~cyclosporine~~ CsA regimens, one with LDS and the other with standard steroid therapy (SST). The primary endpoint was to examine the incidence of rejection following liver transplantation, and to compare graft and patient survival in FK506 with LDS, ~~CyA~~ CsA with LDS, and ~~CyA~~ CsA with SST. One hundred fifty four (154) patients were enrolled between February 17,1990 and December 30, 1991. LDS therapy consisted of one gram of methylprednisolone (MP), while SST consisted of a gram of MP followed by a six day steroid taper, for both induction and treatment of rejection. The patient demographics and results are shown in Table 1. The one year patient and graft survival, as analyzed by intent to treat, was 92% and 88% respectively for FK506, compared to 85% and 79% respectively for ~~cyclosporine~~ CsA. The freedom from rejection was statistically greater in the FK506-treated group, as compared to ~~cyclosporine~~ CsA-treated group.

Table 1

A total of 53 (70%) of patients who were on ~~CyA~~ CsA, were converted to FK506 with LDS immunosuppression. 43 patients because of recurrent or refractory rejection after steroid treatment for rejection, 5 patients for preservation injury, 2 patients following retransplantation, 1 patient for Rh incompatibility, and 1 patient drop out. Only one patient on FK506 was converted to ~~CyA~~ CsA. Of the patients who were converted to FK506, 22 (42%) of patients are on FK506 only (no steroids), as compared to 41% of patients who were randomized to the FK506 limb initially.

The results in this single center study have been compared to two other ongoing randomized liver transplant trials in both the United States and Europe (Fujisawa, personal communication). In each series, over 500 patients were entered into the combined limbs. Using a regimented FK506 treatment arm, the results obtained in the early preliminary results support the findings at the University of Pittsburgh. The European study demonstrated a 15% enhanced patient and graft survival in the FK506 limb, when compared to the ~~CyA~~ CsA limb. Although the patient survival was similar in both groups in the American study, there was a slight benefit in graft survival in the FK506 limb. In both studies, there was less rejection in the FK506 limb, and the overall dosing of steroids was less in the FK506 limb. The results of these studies are still being analyzed and will be officially reported later this year, (1993).

KIDNEY RESCUE TRIALS

The application of FK506 rescue therapy to kidney transplantation was an extension of the experience gained in liver transplantation. The predominant difference between the two organ systems is the predominance of arteriopathy and sclerosis of epithelial structures in the

kidney allografts undergoing chronic rejection. This was found to limit the ability of FK506 to rescue grafts with this pathologic finding. In a series of 35 patients, those with ongoing acute cellular rejection had a successful conversion rate of 71%, while those with stigmata of chronic rejection were not able to be rescued (18). Those with living related kidney transplants had a higher rate of rescue (73%) as compared to those with cadaveric grafts (50%), probably related to an earlier referral for FK506 rescue therapy.

PRIMARY KIDNEY TRANSPLANTATION

FK506 has been utilized as primary baseline immunosuppression in two series of patients. Shapiro and coworkers (19) reported on a series of 234 patients undergoing kidney transplantation with FK506, and compared the results to a concurrent single institution experience with ~~cyclosporine~~ CsA. The patient characteristics and results of the study are shown in Table 2. While the immunologic characteristics of the FK506 group was less favorable as compared to the ~~cyclosporine~~ CsA limb, the results of graft survival and graft function were no different. Nevertheless, the incidence of hypertension and freedom from steroid use was statistically better with the use of FK506, confirming the previous findings with the primary liver transplant experience.

A multicenter study of primary kidney transplantation under FK506 was reported by the Japanese FK506 study group in 1991 (20). In this pilot Japanese experience, 37 kidney transplant patients were given FK506 at fixed doses, and the drug levels correlated with side effects at the conclusion of the study. ~~48%~~ Forty six per cent of the patients experienced a rejection episode, however the majority of patients (84%) were living related

transplants. The three month survival for both grafts and patients was 100%. Toxicity consisted of renal impairment, gastrointestinal complaints, hyperkalemia, tremor, hyperglycemia and chest discomfort, and was associated with a FK506 whole blood level greater than 20 ng/ml.

A randomized trial, utilizing FK506 in a double drug regimen (FK506 and steroids) versus a triple drug regimen (FK506, steroids and azathioprine), was performed in kidney transplantation at the University of Pittsburgh (Shapiro R et al, manuscript in preparation). Two hundred and four ~~204~~ patients were enrolled; there were no specific exclusion criteria based on immunologic or transplant history. Thirty per cent ~~30%~~ of the patients were undergoing a retransplant, with 17% of the recipients being sensitized (PRA>40%). The one year actuarial patient and graft survival rates for the two drug-versus three drug-regimen were: 95% and 90% versus 91% and 82%, respectively. No differences were noted in ~~the~~ kidney function, with the mean serum creatinine of 1.8 ± 0.8 mg/dl. The rejection rate in the three drug regimen was less than that for the two drug regimen (37% vs. 51%), although this was not statistically significant (p=0.07). Crossover from one group to another was not uncommon, 25% of the two drug group were given azathioprine, principally due to rejection, while 45% of the three drug group required discontinuation of azathioprine because of leucopenia or hepatic dysfunction.

HEART TRANSPLANTATION

Armitage and coworkers at the UPMC ~~University of Pittsburgh~~ have reported their experience with FK506-based immunosuppression following heart transplantation (21,22). In 8 patients, FK506 was utilized as rescue therapy for patients suffering from persistent, refractory cardiac

rejection on ~~cyclosporine~~ CsA, azathioprine and steroids (21). All of these 8 patients had received and failed one or more courses of antilymphocyte therapy while of ~~cyclosporine~~ CsA therapy. In keeping with the previous experiences with rescue therapy, all of these patients had demonstrated improvement in the histopathology after FK506 conversion.

~~72~~ Seventy two primary adult patients were given FK506 as primary immunosuppression following heart transplantation (22). The one year patient and graft survival was 92% (Figure 1). The overall rejection rate was 67%, with 33% of these patients not having any rejection. The freedom from rejection at 90 days was 41% and at 180 days was 34%. Renal dysfunction was frequently noted, and the mean serum creatinine at 6 months following transplantation was 2.2 mg/dl. The incidence of diastolic hypertension was 54%, but was considered mild, as treatment consisted of a single agent in all cases. The incidence of new onset diabetes was 20% in this group of patients.

INTESTINAL TRANSPLANTATION

One way to assess the impact of a new immunosuppressive agent in transplantation, is the ability to successfully transplant organs, which were not considered feasible with standard immunosuppression. This was certainly the situation when ~~cyclosporine~~ CsA was introduced to liver transplantation (23). Success with intestinal transplantation under ~~cyclosporine~~ CsA immunosuppression has been sporadic (24-26).

A growing experience of small bowel transplantation, either alone, or combined with other abdominal organs, has been accumulated under FK506 at the ~~University of Pittsburgh~~ UPMC (27-30). Small bowel allografts have been transplanted alone (n=9), together with liver (n=16), or as part

of a multivisceral cluster (n=3). In these 28 patients, 82% were alive at a median followup of 9 months. Graft survival was 76% at the same period of time. Graft function was satisfactory, with 84% of survivors ~~being~~ showing ~~totally~~ complete enteral sufficiency, and the other 16% relying on supplemental parenteral nutrition. Rejection was not uncommon, with 90% of the patients having at least one rejection episode of the intestinal allograft. Rejection has been treated by additional steroids and addition of azathioprine; however, anti-lymphocyte preparations have been used occasionally.

LUNG TRANSPLANTATION

A small experience of pediatric lung transplantation under FK506 has been reported by Armitage and coworkers (31). Eleven patients received FK506, two of whom have died because of early infectious complications. While rejection episodes were no different between FK506 and ~~cyclosporine~~ CsA, unlike the ~~cyclosporine~~ CsA experience, antilymphocyte preparations have not been required to reverse rejections on FK506. In addition, hypertension was not seen in the FK506 group, as compared to an incidence of 50% in the ~~cyclosporine~~ CsA group.

A prospective randomized trial of primary adult pulmonary transplantation was conducted at the ~~University of Pittsburgh~~ UPMC (Griffith BP et al, manuscript in preparation). Azathioprine was combined with either FK506 or ~~cyclosporine~~ CsA, resorting to using steroids only if the recipient encountered more than one episode of rejection. ~~29~~ Twenty eight patients were randomized to FK506; 29 patients were randomized to ~~cyclosporine~~ CsA. The six month graft survival was statistically better in the FK506 group as compared to the ~~cyclosporine~~ CsA group (86% vs. 69% respectively, $p<0.05$).

Twenty one per cent
~~21%~~ of the FK506 patients were rejection free at 6 months, as compared to only 3% of the ~~cyclosporine~~ CsA patients.

OTHER FK506 ISSUES

The results of these studies suggest that FK506 is effective for solid organ transplantation. The dosing schedule and monitoring techniques for FK506 continue to be modified. One of the principle issues regarding the use of FK506 has been with monitoring of drug levels. In Europe and at other centers in the United States, whole blood levels have been utilized. This measures not only plasma levels (the assay utilized at our institution), but also cell-bound FK506. The principle advantage of whole blood levels are the higher FK506 levels which can be detected, making adjustments in FK506 dosing potentially easier. In addition, whole blood monitoring offers the advantage of faster analysis times and less variability of sample storage and preparation disparity. We are currently measuring both whole blood levels and plasma levels in order to gain clinical experience utilizing FK506 whole blood monitoring.

DISCUSSION

While impressive gains in patient and graft survival have been obtained in solid organ transplantation, rejection continues to play a significant role in morbidity and mortality. A search for new immunosuppressive agents must be able to impact on the rates and severity of rejection. Ample clinical reports correlate the adverse impact of rejection on long term graft survival. In the clinical trials presented here, FK506 appears to provide a baseline immunosuppression which is more potent than ~~cyclosporine~~ CsA. At our institution, this is correlated with

that achieved with

enhanced patient and graft survival at one year. In addition, the impact of FK506 on previously "forbidden" transplantation, has been dramatic, with the introduction of a successful intestinal transplantation program and enhanced results of lung transplantation.

We have reported encouraging clinical trials with ~~a~~ the new immunosuppressive agent ~~called~~ FK506, ~~which is~~ a macrolide antibiotic produced by the fungus, Streptomyces tsukubaensis ~~(32)~~ (3). The molecular structure of FK506 is unrelated to ~~cyclosporine~~ that of CsA, and the 2 drugs have different cytosolic binding sites ~~(33,34)~~ (32,33). However, both drugs inhibit T-lymphocyte activation, in part by suppressing the synthesis and expression of the cytokine, interleukin-2 ~~(35,36)~~ (34,35). Yet there is a practical difference in the utilization of these agents. The ability of FK506 to be used to reverse ongoing, established rejection, is not a characteristic of ~~cyclosporine~~ CsA. The dose adjustability of FK506 allows the physician to titrate the immunosuppressive baseline to the threshold of rejection, rather than to arbitrarily rely on target drug levels, which may represent overimmunosuppression for some, and underimmunosuppression for others.

FK506 is not without its limitations. Toxicity profiles for FK506 are similar to ~~that~~ those of ~~cyclosporine~~ CsA, perhaps because of similiar mechanisms of action. A detailed analysis and review of the adverse effects of FK506 is beyond the scope of this discourse. Readers are referred to detailed reports of FK506 adverse effects ~~(37,38)~~ (36,37). Both FK506 and ~~cyclosporine~~ CsA administration ~~have~~ has been associated with side effects, many of which are similar, and some of which are peculiar to a given organ transplant.

A detailed analysis of all major adverse events was completed in 370 consecutive primary liver transplant recipients ~~(37)~~ (36). The one year

patient and graft survival in this series was 85% and 77% respectively. Pretransplant renal dysfunction was seen in 31 (9%) of patients, of which 23 required preoperative hemodialysis. Early onset renal dysfunction was defined as a rise in the serum creatinine to >3 mg/dl in the first 30 days after transplant. This occurred in 40% of patients, ~~of which~~ Half of these events were ascribed to FK506 toxicity and the remainder to other coexistent factors. The incidence of patients requiring hemodialysis following liver transplantation was twice as high in the later group than in patients with only FK506 nephrotoxicity. Most of the patients with early post-transplant renal dysfunction returned to normal levels within 30 days ~~after~~ of the transplant~~ation~~. The incidence of chronic renal failure (defined as a serum creatinine >2.0 mg/dl) at 12 months following transplant was 20.5%. The incidence appeared stable after 6 months following transplant. The incidence of renal failure requiring chronic hemodialysis was 1.2% in this study.

Long-term hyperkalemia was seen in 37% of patients treated with FK506 and was generally treated with potassium binding resins and potassium restricted diets. Addition of a synthetic mineralocorticoid, Florinef, relieved the hyperkalemia by increasing potassium excretion by the kidney.

Alterations in glucose metabolism are the result of changes in peripheral sensitivity to insulin and/or changes in the response of the islet cells to hyperglycemia. The incidence of permanent new onset diabetes, i.e. those patients requiring insulin, was 11.2% in liver transplant patients. The long-term consequence of insulin requirement in transplant patients, towards the development of diabetic complications is not known.

Rare but severe instances of neurotoxicity have been reported following FK506 administration. Thirty one episodes of neurotoxicity were seen in the 370 liver transplant patient study. New onset seizures were reported in 12 liver transplant patients, especially during the perioperative transplant period (incidence of 3%). The susceptibility of such patients to changes in serum electrolytes has been previously reported. Delirium was noted in 11 patients (incidence of 3%). Persistent coma was noted in 4 patients (incidence of 1%). Expressive aphasia has been seen in five liver transplant patients (1% incidence). In all but one case, the neurologic findings were reversible.

Post-transplant lymphoproliferative disease (PTLD) is an abnormality of lymphocyte proliferation in the setting of an immunosuppressed patient. The spectrum of PTLD can range from a benign lymphoid proliferation, such as a mononucleosis syndrome, to a frankly malignant lymphoid tumor. PTLD has been associated with all types of immunosuppressive therapy. The incidence of PTLD in the CsA era is generally estimated between 2% and 4%. The median time following transplantation to the development of PTLD is 6 months, while the majority of these tumors occur within 12 months following transplantation.

The cumulative incidence of patients developing de novo PTLD lesions while on FK506 therapy is approximately 2%. All of the cases of PTLD occurred within the first year following initiation of FK506, with the median time from FK506 therapy to onset of disease being 4 months. FK506 shows no evidence of increasing the risk of developing or succumbing to PTLD, when compared to other immunosuppressive

regimens. No patients treated with FK506 for non-transplanted indications have developed any malignancies.

Cytomegalovirus (CMV) infections are considered the most common opportunistic infection in the transplant patient. Several factors determine the severity and development of CMV infections. ~~The~~ Seronegativity and the use of intensive immunosuppression are considered major contributing factors. The incidence of CMV infections in the FK506 treated transplant patients is 20%. This figure is similar to that seen in transplanted patients on CsA. ~~cyclosporine~~. No patients treated with FK506 for non-transplant indications have developed CMV infections.

Because FK506 is an investigational drug, all of the side effects/risks of this drug are as yet, unknown. In particular, the effect of FK506 on fertility and on the fetus is not known. Of the 12 female patients treated with FK506 who became pregnant, there were 2 fetal losses, one from CMV infection and the other from premature delivery (24 weeks). The 10 other babies are healthy and without birth defects.

Combinations of immunosuppressive agents, including agents acting on different aspects of the efferent or afferent immune limbs, may minimize the side effects of any particular agent. Current and future trials using conventional or other experimental agents along with FK506 may allow further refinement and individualization of immunosuppressive regimens.

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FIGURE LEGEND

FIGURE 1: Kaplan Meier estimate of patient survival following adult cardiac transplantation under FK506 immunosuppression.

Table 1: Patient Characteristics and Results of FK506 vs. Cyclosporine Randomization for Primary Liver Transplantation

Parameter	FK506	Cyclosporine		
		Total	LDS	SST
Number of patients	78	76	40	36
Age (median; years)	43	42		
Diagnosis				
Biliary Cirrhosis	13	16		
Hepatocellular	65	60		
Median F/U (d)	611	594	700	402
Deaths	7	9	7	2
Retransplants	7	11	8	3
Rejection-Free				
Actual (current)	34	7	2	5
One month after	39	16	7	9
Switch	1	53	32	21
Steroid-Free	32	1		

F/U (d) = median follow-up (days)

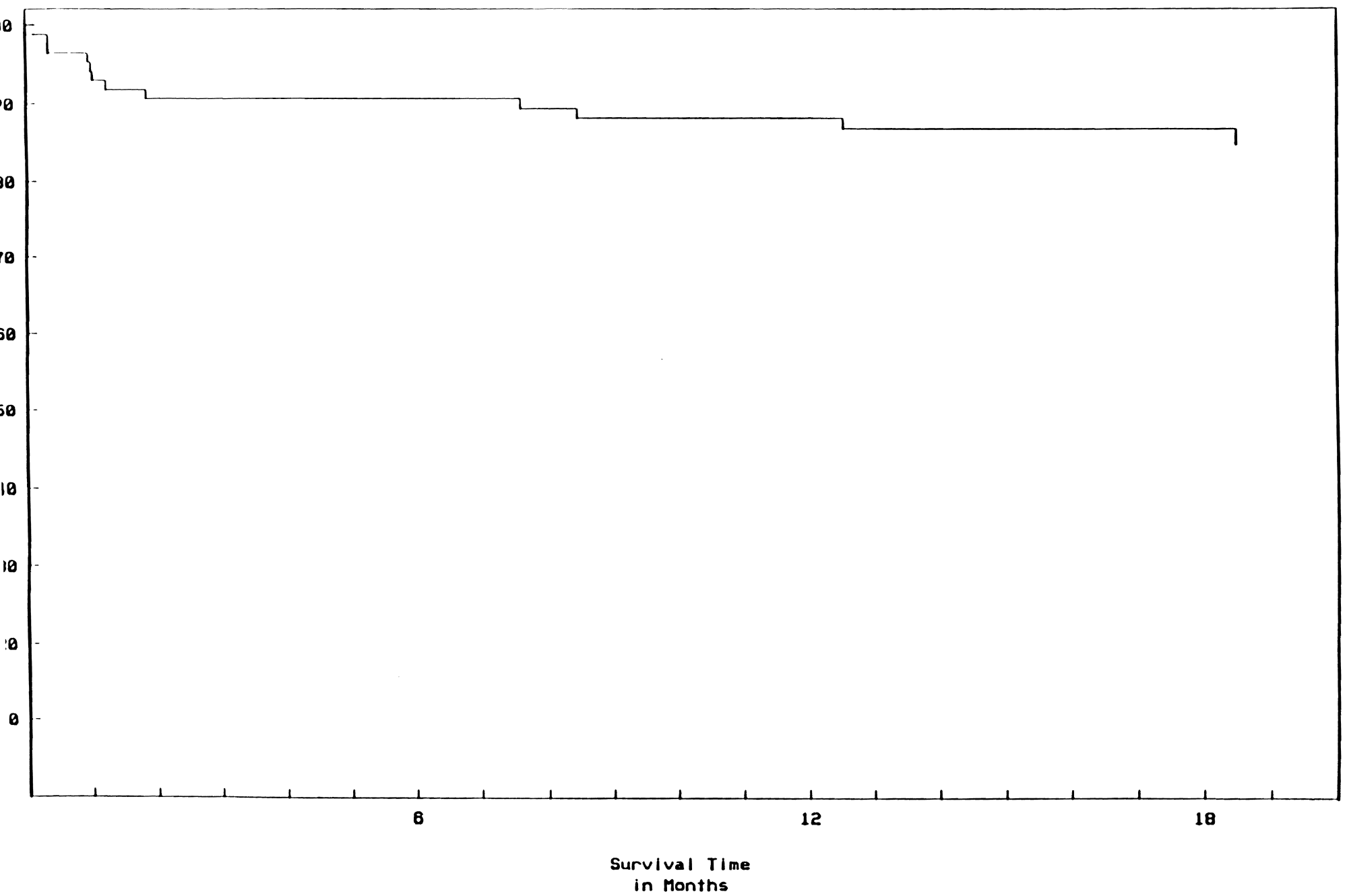
LDS = low dose steroids

SST = standard steroid taper

Table 2: Patient Characteristics and Results of FK506 vs. Cyclosporine for Primary Kidney Transplantation

Parameter	FK506	Cyclosporine
Number of patients	234	191
Age (median; years)	41	38
Previous Transplant	76 (32%)	38 (19%) *
PRA >40%	41 (17%)	26 (13%)
Living Related	12 (5%)	28 (14%)
1 yr. Patient Survival	90%	94%
1 yr. Graft Survival	74%	77%
Creatinine (mg/dl)	2.1	1.9
Freedom from Steroids	44%	0%*
Freedom from Hypertension	43%	25%*

*$p<0.05$

PRA = panel reactive antibodies

Survivorship Function
FK506 ADULT HEART RECIPIENTS