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FK506 IN PEDIATRIC KIDNEY TRANSPLANTATION - PRIMARY AND RESCUE EXPERIENCE

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ABSTRACT

Between December 14, 1989, and December 17, 1993, 43 patients undergoing kidney transplantation alone at the Children's Hospital of Pittsburgh received FK506 as the primary immunosuppressive agent. The mean recipient age was 10.2 ± 4.8 years (range 0.7 - 17.4), with 7 (16%) children under 5 years of age and 2 (5%) under 2 years of age. Fifteen (35%) children underwent retransplantation, and 5 (12%) had a panel reactive antibody level greater than 40%. Twenty-two (51%) cases were with cadaveric donors, and 21 (49%) were with living donors. The mean follow-up is 25 ± 14 months. There were no deaths. One and three year actuarial graft survival was 98% and 85%. The mean serum creatinine and BUN were 1.2 ± 0.6 mg/dl and 26 ± 11 mg/dl; the calculated creatinine clearance was 75 ± 23 ml/min/1.73 m^2. Twenty-four (62%) patients have been successfully withdrawn from steroids, and 24 (62%) require no anti-hypertensive medication. Improved growth was seen, particularly in pre-adolescent children off steroids.

Between July 28, 1990, and December 2, 1993, 24 children were referred for rescue therapy with FK506, 14.6 ± 16.4 months (range 1.1 - 53.2) after transplantation. Nineteen (79%) were referred because of resistant rejection; 4 (17%) were referred because of proteinuria; 1 (4%) was switched because of steroid-related obesity. There were no deaths. One and two year graft survival was 75% and 68%. Seventeen (71%) patients were successfully rescued, including 1 of 2 patients who arrived on dialysis. Four (24%) of the successfully rescued patients were weaned off steroids.

While not without side effects, which include nephrotoxicity, neurotoxicity, diabetogenicity, and viral complications, FK506 appears to be an effective immunosuppressive agent for both primary and rescue therapy after kidney transplantation. Its steroid-sparing qualities may be of particular importance in the pediatric population.

INTRODUCTION

FK506 (Tacrolimus - trade name Prograf®) is a new immunosuppressive agent isolated from the soil organism Streptomyces Tsukubaensis. It has well described in vitro and experimental in vivo immunosuppressive properties[1], and has been used in clinical heart[2], lung[3], liver[4], kidney[5-9], intestinal[10], and islet[11] transplantation. The initial experiences in pediatric kidney transplantation have been previously described.[12-16] Patient and graft survival have been comparable to that seen under cyclosporine immunosuppression, but lower steroid and antihypertensive requirements have been observed with FK506.[14-16] In addition, improved growth has been demonstrated in certain subgroups of children on FK506.[14] Of some concern has been the suggestion of a higher incidence of viral complications associated with FK506, although they have all resolved without graft loss or patient death.[15,16]

FK506 has also been used in an attempt to salvage patients transplanted under cyclosporine immunosuppression.[17,18] The most common indication has been resistant acute rejection, and a success rate of 70 - 75% in unselected adults and children has been achieved. Most of these patients have received one or more courses of antilymphocyte therapy, and a smaller number of patients were on or had returned to dialysis prior to the initiation of rescue therapy.

In this paper, we summarize our experience to date with both primary and rescue therapy with FK506 in pediatric kidney transplantation.

PATIENTS AND METHODS

Primary Group

Forty-three consecutive patients undergoing 43 kidney transplantations only at the Children's Hospital of Pittsburgh between 12/14/89 and 12/17/93 and receiving FK506 as the primary immunosuppressive agent were available for analysis (Table 1). Patients undergoing concomitant or previous liver transplantation were excluded. The mean recipient age was 10.2 ± 4.8 (range 0.7 - 17.4) years; 7 (16%) were under 5 years, and 2 (5%) were under 2 years of age. There were 28 (65%) boys and 15 (35%) girls. Twenty-eight (65%) patients were receiving their first transplant, and 15 (35%) were undergoing retransplantation. Just over half of the retransplant cases had been previously transplanted at other centers. Five (12%) patients (all retransplants) had a panel reactive antibody level greater than 40%. The causes of end stage renal disease are listed in Table 2.

Twenty-two (51%) patients received kidneys from cadaver donors with a mean cold ischemia time of 31.2 ± 8.6 (range 12.1 - 45.1) hours, and an average HLA antigen match of 2.1 ± 1.3 and mismatch of 3.6 ± 1.2. There was one (5%) 6 antigen match. Five (23%) donors were 1 - 5 years of age. In two cases, the donors were 1 and 1.2 years old, and both kidneys were transplanted en bloc; in the other 3 cases, single kidneys from donors 3, 4, and 5 years of age were transplanted. The recipients of these pediatric kidneys were older children, 10.3 - 16.7 years of age. Twenty-one (49%) patients received kidneys from living donors; there were 19 parents, 1 grandmother, and 1 adoptive father. The mean donor age was 29.6 ± 15.1 (range 1 - 50) years for all patients.

Immunosuppression was with FK506 and steroids, as has been described

previously;[15,16] azathioprine was also used initially in 18 (42%) patients. Induction therapy with antilymphocyte preparations was not used, although it was administered for steroid-resistant rejection episodes. Over 90% of rejection episodes were biopsy-proven.

Rescue Group

Between July 28, 1990, and December 2, 1993, twenty-four patients were admitted to the Children's Hospital of Pittsburgh for FK506 rescue, 14.6 ± 16.4 (range 1.1 - 53.2) months after transplantation (Table 3). The mean age at the time of transplantation was 10.7 ± 4.5 (range 0.6 - 16.8) years. Twenty (83%) patients had undergone their first transplant, and 4 (17%) had undergone retransplantation. Nineteen (79%) had received kidneys from cadaveric donors, and 5 (21%) had received kidneys from living related donors. Nineteen (79%) patients had experienced acute rejection resistant to both steroids and antilymphocyte preparations. Four (17%) were switched because of proteinuria after transplantation[19], and 1 (4%) was switched in an attempt to reduce steroid-related obesity. Three (12%) patients had been transplanted at the Children's Hospital of Pittsburgh; the remaining 21 (88%) patients had been transplanted at 11 other centers in United States.

In general, switch-over was from oral cyclosporine to oral FK506 0.15 mg/kg twice daily; the patient's azathioprine and prednisone dosage were not initially changed. The FK506 dosage was then adjusted according to the levels; where possible, azathioprine and prednisone dosages were reduced after renal function had stabilized.

Statistical Analysis

For the primary FK506-treated group, patient survival was calculated from the date of kidney transplantation until death, and graft survival from the date of kidney

transplantation until graft failure, retransplantation, or patient death. Survival curves were generated using the Kaplan-Meier (product limit) method and were compared using the logrank (Mantel-Cox) test. All tests were two-tailed. A p-value less than 0.05 was considered statistically significant.

For the rescue group, patient survival was calculated from the date of initiation of FK506 until death, and graft survival from the date of initiation of FK506 until graft failure, retransplantaion, or patient death. Cox's proportional hazards model was used to calculate the actuarial graft survival, taking into account the median time, after kidney transplantation, when FK506 was started.

The standard two-sample t-test was used to test differences between means, while differences in proportion were tested using Pearson's Chi-square test of association. The Wilcoxon Rank Sum test, a non-parametric equivalent to the standard two-sample t-test was used for highly skewed data.

RESULTS

Primary Group

The mean follow-up is 25 ± 14 months. All patients are alive. The overall one- and three-year actuarial graft survival is 98% and 85% (Figure 1). Four kidneys have been lost, at 0.3, 13.5, 20.7, and 29.0 months, to recurrent hemolytic uremic syndrome, rejection, non-compliance, and recurrent membranoproliferative glomerulonephritis, Type II. The one- and three-year actuarial graft survival for specific subgroups is shown in Table 4. Of note, all the kidneys from the donors 5 years of age or younger are functioning well 9 - 52 months after transplantation.

The mean serum creatinine and BUN were 1.2 ± 0.6 mg/dl and 26 ± 11 mg/dl. The calculated creatinine clearance was 75 ± 23 ml/minute/1.73m^2.[20]

The incidence of early non-function was 7.0%; 2 (5%) patients required dialysis after transplantation.

Acute rejection was seen 25 (58%) patients; antilymphocyte therapy was required in 3 (7%) patients. Eighty-eight percent of the rejections were steroid-responsive. The incidence of rejection was not statistically different between living donor (67% - 14/21) and cadaver donor (50% - 11/22) (p=0.27) cases. The incidence in rejection in children less than 5 years of age, between 5 and 10 years, and greater than 10 years, was 57%, 53%, and 62% (p=ns). In patients receiving triple drug therapy with azathioprine, the incidence of rejection was 61%; in those patients starting on double drug therapy, the incidence was 56%.

Cytomegalovirus was seen in 6 (14%) patients and was treated with intravenous gancyclovir. Post-transplant lymphoproliferative disorder (PTLD) was seen in 5 (12%) patients and was treated with reduction or temporary cessation of immunosuppression and intravenous gancyclovir or acyclovir. In addition, 1 patient developed Epstein-Barr virus gastritis without PTLD was treated with gancyclovir and reduction of immunosuppression, and 1 patient developed a transient liver lesion that was not proven to be PTLD but disappeared with reduction of immunosuppression. No grafts were lost in the process of treating these complications, and all patients recovered.

Transient new onset diabetes mellitus was seen in 3 (7%) patients and disappeared with reduction in the FK506 and steroid dosages.

The mean dosage of FK506 was 0.19 ± 0.15 mg/kg/d. The mean level was 0.56 ±

0.33 ng/ml.

24 (62%) patients have had maintenance steroids discontinued. 3 (8%) additional patients have had steroids discontinued and then resumed because of rejection. The overall mean prednisone dose is 3.0 ± 5.0 mg/d (0.1 ± 0.1 mg/kg/d). The mean prednisone dose in those patients still on steroids is 7.1 ± 4.8 mg/d (0.2 ± 0.1 mg/kg/d).

The growth patterns in patients on and off steroids are shown in Table 5. In general, there was a trend toward improving Z scores over time in all patients; not surprisingly, this was more pronounced in those children who were off steroids. When the analysis was further subdivided into pre-adolescents and adolescents, the most striking growth improvement was in the pre-adolescent children off steroids. This is in accord with our previous observations,[14] but the magnitude of improvement in growth is more pronounced. At most recent follow-up, the Z score for the pre-adolescents off steroids was + 0.92.

24 (62%) patients are off antihypertensive medications. The mean serum cholesterol is 178 ± 53 mg/dl.

Rescue Group

The mean follow-up, after initiation of FK506 is 20.3 ± 11.7 months. None of the 24 patients died after beginning rescue therapy. The one and two-year actuarial graft survival is 75% and 68% (Figure 2). 7/24 (29%) patients have unequivocally failed FK506 rescue therapy and have returned to dialysis, representing a success rate of 71%. For patients undergoing rescue for rejection, the success rate was 74% (14/19); for those patients with proteinuria, it was 50% (2/4); and the 1 patient with steroid-associated obesity was successfully switched and withdrawn from steroids. The success rate for cadaver and

living donor kidney recipients was 74% (14/19) and 60% (3/5), respectively. 13/20 (65%) of patients undergoing their first transplant was successfully rescued and 4/4 (100%) of the retransplant patients were switched successfully. Two patients were on dialysis at the time of initiation of rescue therapy, and 1 was successfully rescued.

The mean serum creatinine prior to and after rescue was 2.0 ± 1.2 mg/dl and 1.9 ± 1.0 mg/dl; the corresponding BUN was 42 ± 38 and 32 ± 11. Calculated creatinine clearance was 47.1 ± 27.9 ml/min/1.73m^2 and 51.5 ± 19.3 ml/min/1.73m^2. The dosage of FK506 was 0.25 ± 0.14 mg/kg/d; the level was 0.67 ± 0.45 ng/ml. The mean prednisone dose before and after rescue was 16.8 ± 10 and 5.4 ± 5.0 mg/d ($p=0.01$). 4 (24%) patients have been weaned off prednisone after successful rescue.

There was 1 case of cytomegalovirus in the rescue group that was diagnosed at the time of transfer for switchover to FK506. Gancylovir was administered, and FK506 was started; the patient recovered uneventfully. There was one case of PTLD occurring within one month after switchover; immunosuppression was discontinued, and the patient was treated with gancyclovir. The PTLD resolved, but the allograft was lost.

DISCUSSION

The evaluation of new immunosuppressive agents is more difficult than it was 10 - 15 years ago, because of the better results achieved with cyclosporine-based regimens. In fact, our recent retrospective comparison of cyclosporine and FK506 in pediatric kidney transplantation demonstrated comparable patient and graft survival; the big difference was in the ability to discontinue steroids in over half of the FK506-treated patients, and in the associated improvement in growth.[14-16] The current update confirms the ability to wean a

substantial number of children off steroids under FK506 immunosuppression. The resultant improvement in growth makes FK506 a particularly attractive agent in pediatric transplantation.

Unfortunately, an important complication seen initially with FK506 in pediatric renal transplant recipients was an increase in viral complications, including PTLD. Fortunately, these complications all resolved without patient or graft loss. With increasing experience, the incidence of significant viral complications has decreased, and there have been no new cases of PTLD in the patients transplanted in the past year.

There is little question that FK506 is a nephrotoxic agent[21-23]; this toxicity seems comparable to that seen with cyclosporine.[24,25] It is noteworthy that, in a protocol that did not employ induction therapy and that used intravenous FK506, the incidence of early nonfunction requiring dialysis was only 5%.

Rejection has remained an important problem in our pediatric renal transplant population receiving FK506, with an incidence of 58%. While 88% of these rejections are steroid-responsive, and only 1 kidney has been lost to rejection, the overall incidence is still high. We have used a third agent, azathioprine, as an attempt to reduce the incidence of acute rejection, but have not seen any benefit. Parenthetically, in a prospective randomized trial in adult renal transplant recipients, a comparison of FK506 and prednisone with FK506, azathioprine, prednisone showed somewhat less acute rejection in the triple drug group but no improvement in graft survival.[9] Sequential four drug therapy is being used in an ongoing multicenter randomized trial comparing FK506 and cyclosporine, and it will be useful to see whether the use of induction antilymphocyte therapy with FK506 will reduce the incidence

of acute rejection. In addition, there are a number of new immunosuppressive agents that are being evaluated, such as RS61443[26], Brequinar[27], Rapamycin[28], Leflunomide[29], and 15-Deoxyspergualin[30]; perhaps one or more of these agents, in combination with FK506, will be effective in helping to reduce the incidence of acute rejection.

The use of FK506 to rescue rejecting renal allografts or to turn off proteinuria after transplantation remains a bit mysterious. The success rate of 71% is the same as that reported in the larger series reported by Jordan et al.[17,18] The success rate might conceivably have been higher but for a fairly broad willingness to accept patients for rescue therapy. Until the spring of 1994, FK506 remained investigational, and the ability to use it as a rescue agent for renal transplantation patients was limited, with few exceptions, to a single center. There has been a tendency, therefore, to accept virtually all patients referred, because of the perception that conversion to FK506 was the last hope. In the process, patients with fairly significant scarring have been switched over, with less than satisfactory results. As has been detailed in previous papers, fibrosis or chronic rejection are relative contraindications for switchover to FK506 in renal transplant patients.

That having been acknowledged, the ability to salvage the majority of patients and restore good renal function to a child who arrived on dialysis remains difficult to understand. Our understanding of the mechanism of action of FK506, in blocking the initiation of IL-2 mRNA transcription, does not per se explain its ability to reverse rejection in renal and other solid organ allografts. There may well be some anti-rejection property of the agent is, as yet, not well understood. In any event, the clinical phenomenon is real and has helped salvage a number of patients. Where it has failed, the reasons have been unremitting

rejection, extensive prior scarring or other chronic changes, or proteinuria secondary to irreversible morphologic changes. A few of the early successes have gone on to have some deterioration in renal function, related, in some cases, to noncompliance, or in other cases, to the presence (or perhaps progression) of chronic processes. Fortunately, no deaths have been ascribed to FK506 rescue in the pediatric renal transplant population.

The next ten years will see major changes in the immunosuppressive armamentarium, as more agents pass through the investigative pipeline and are approved for clinical use. The number of possible drug combinations will be large, and sorting out the most effective ones will be a complex process. It is clear, based on its immunosuppressive efficacy as a primary and rescue agent, and its steroid-sparing capability, that FK506 will be one of the most important of these new agents. The challenge will be to develop the ways to minimize its nephrotoxicity and not sacrifice its immunosuppressive advantages.

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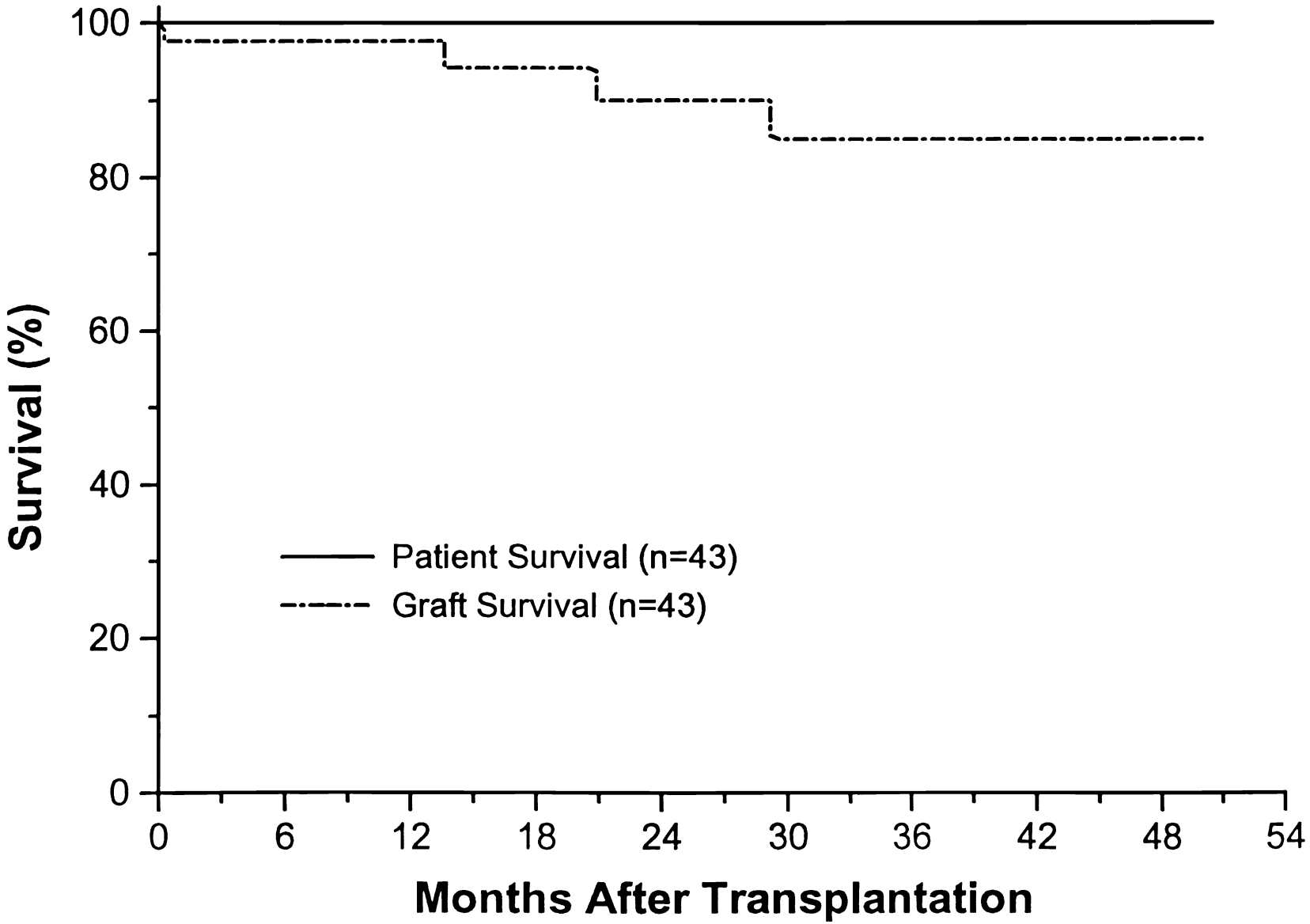
FIGURE LEGENDS

Figure 1: Pediatric Kidney Transplantation Under FK506. Primary Group - Patient and Graft Survival.

Figure 2: Pediatric Kidney Transplantation Under FK506. Rescue Group - Patient and Graft Survival.

Pediatric Kidney Transplantation Under FK506
Primary and Rescue Experience
Primary Group - Patient and Graft Survival



Pediatric Kidney Transplantation Under FK506

Primary and Rescue Experience

Rescue Group - Patient and Graft Survival

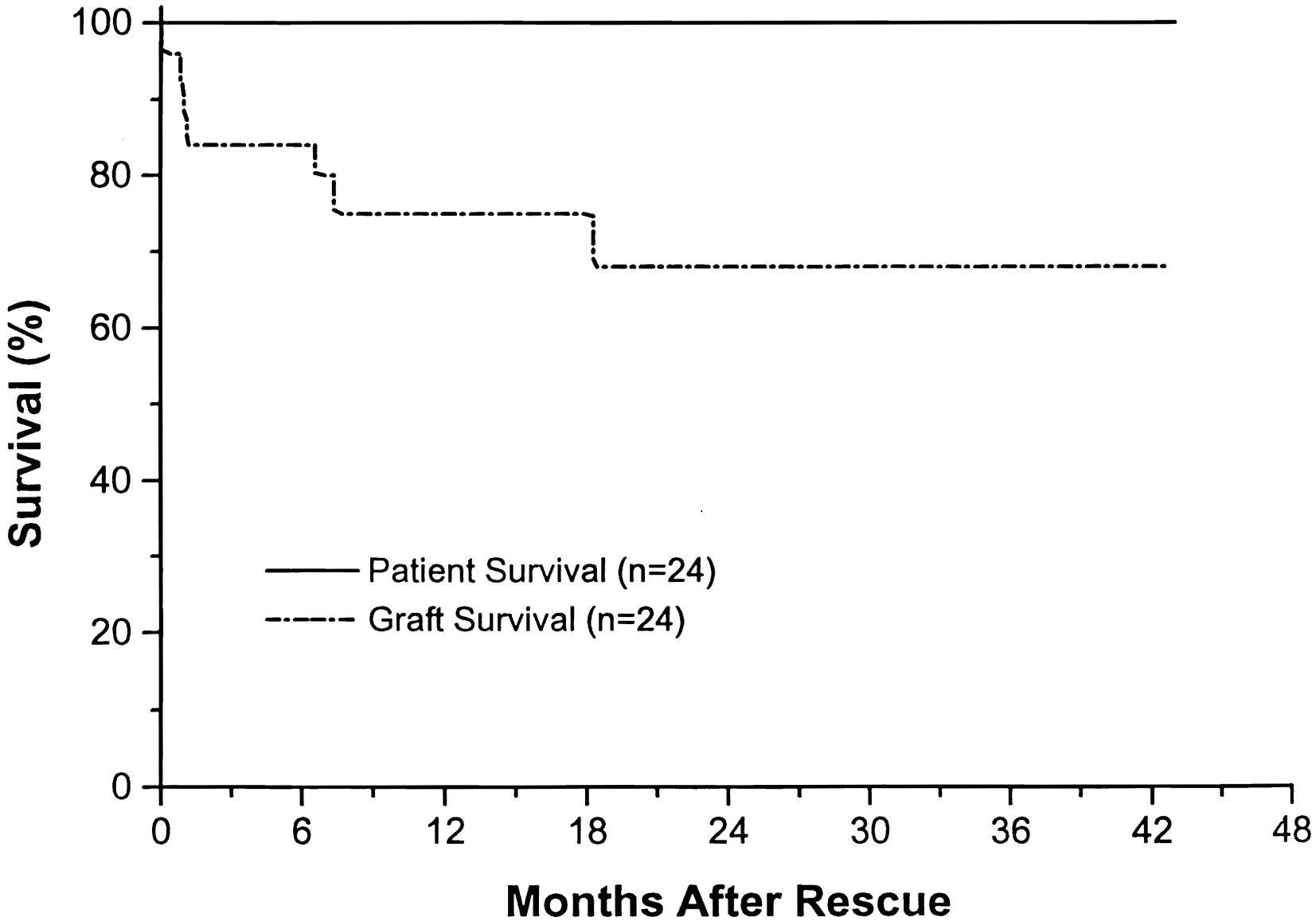


TABLE 1

PRIMARY GROUP - RECIPIENT DEMOGRAPHICS

N	43
Age	10.2 ± 4.8 years (range 0.7 - 17.4)
Under 5 Years	7 (16%)
Under 2 Years	2 (5%)
M/F	28 (65%)/15 (35%)
First Transplant	28 (65%)
Retransplant	15 (35%)
PRA < 40%	38 (88%)
PRA > 40%	5 (12%)
Cadaver Donor	22 (51%)
Living Donor	21 (49%)

TABLE 2

PRIMARY GROUP - CAUSES OF END STAGE RENAL DISEASE

Glomerulonephritis	6 (14%)
Obstructive Uropathy	5 (12%)
Congenital Dysplasia	5 (12%)
FSGS	5 (12%)
HUS	4 (9%)
Prune Belly	3 (7%)
Congenital Hypoplasia	2 (5%)
Polycystic Kidney	2 (5%)
Cystinosis	1 (2%)
Nephronophthisis	1 (2%)
IgA Nephropathy	1 (2%)
Alport's	1 (2%)
Reflux	1 (2%)
Other	5 (12%)
Unknown	1 (2%)
	43

TABLE 3

RESCUE GROUP - RECIPIENT DEMOGRAPHICS

N	24
Age (At time of transplantation)	10.7 ± 4.5 years (range 0.6 - 16.8)
Time to Rescue (after transplantation)	14.6 ± 16.4 months (range 1.1 - 53.2)
M/F	10 (42%)/14 (58%)
First Transplant	20 (83%)
Retransplant	4 (17%)
Cadaver Donor	19 (79%)
Living Donor	5 (21%)
Indication	
Rejection	19 (79%)
Proteinuria	4 (17%)
Obesity	1 (4%)
Transplant Center	
Pittsburgh	3 (12%)
Elsewhere	21 (88%)

TABLE 4

PRIMARY GROUP - ACTUARIAL SURVIVAL

	1 Year	3 Year
Patient Survival		
Overall	100%	100%
Graft Survival		
Overall	98%	85%
Cadaveric	95%	88%
Living Donor	100%	84%
Recipients < 2 years	100%	100%
>2, < 5 years	80%	80%
> 5 years	100%	86%
Rejection	100%	80%
No Rejection	94%	94%

TABLE 5

PRIMARY GROUP - GROWTH PATTERNS

Z-score (± sd)

	OVERALL	ON STEROIDS	OFF STEROIDS
At Transplant	-2.40 (± 1.58)	-2.22 (± 1.80)	-2.54 (± 1.27)
3 Months	-2.04 (± 1.37)	-2.17 (± 1.10)	-1.94 (± 1.55)
6 Months	-1.46 (± 1.57)	-1.76 (± 1.32)	-1.30 (± 1.70)
1 Year	-0.65 (± 1.89)	-0.94 (± 1.48)	-0.55 (± 2.03)
Most Recent	-0.31 (± 2.02)	-0.92 (± 1.71)	+0.11 (± 2.41)

	ON STEROIDS		OFF STEROIDS	
	≤ 12 Years	> 12 Years	≤ 12 Years	> Years
Time				
At Transplant	-1.9 (± 1.2)	-3.0 (± 1.1)	-2.7 (± 1.3)	-2.3 (± 2.6)
3 Months	-1.7 (± 0.9)	-2.9 (± 1.0)	-1.5 (± 0.7)	-2.6 (± 2.3)
6 Months	-1.2 (± 1.2)	-2.7 (± 1.1)	-0.8 (± 0.8)	-2.1 (± 2.5)
1 Year	-0.4 (± 1.1)	-2.1 (± 1.1)	-0.02 (± 1.7)	-1.6 (± 2.4)
Most Recent	-0.42 (± 1.7)	-2.0 (± 1.1)	+0.92 (± 1.64)	-1.4 (± 2.3)