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RENAL TRANSPLANTATION AT THE UNIVERSITY OF PITTSBURGH: THE IMPACT OF FK-506

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Introduction

FK-506 (Tacrolimus/Prograf ™) is a new immunosuppressive agent recently approved by the Food and Drug Administration. Although it is formally indicated for use only in patients undergoing orthotopic liver transplantation,[1-4] it has been used clinically after transplantation of essentially all solid and hollow organs,[5-7] and both bone marrow[8,9] and pancreatic islets.[10] It has been used for over 5 years in renal transplant patients, both as the primary immunosuppressive agent,[11-16] and in an attempt to rescue failing kidneys.[17] This chapter will summarize our clinical experience with adult and pediatric renal transplant patients, both in the primary and rescue setting, and will touch also on our series of bone marrow augmentation.[18] We hope to demonstrate that FK-506 is an excellent immunosuppressive agent for patients undergoing renal transplantation and that it represents formidable addition to our armamentarium.

Early Experience

The first 2 years' experience with FK-506 in renal transplant patients included a pilot series, a small randomized trial comparing FK-506 with Cyclosporine, and a larger group of patients not eligible for the randomized trial who were given the choice

of receiving FK-506. The latter group included a disproportionately high percentage of patients undergoing retransplantation who had failed conventional therapy in the past, often at other centers. These 240 cases were compared with a roughly concurrent group of 196 cases managed with conventional Cyclosporine-based immunosuppression.[19] The patients in the randomized trial were also analyzed separately, with similar outcomes to the larger group. Comparable patient and graft survival were seen between FK-506 and Cyclosporine treated patients. (Table 1) However, over 40% of the patients on FK-506 were able to be taken off prednisone, and antihypertensive medication requirements were lower in the FK-506 group. In addition, serum cholesterol levels were significantly lower in the FK-506 treated patients. The conclusion of this early work, a time when the dosing and toxicities were still being evaluated, was that FK-506 was certainly as effective as conventional therapy and might have some advantages with regard to secondary issues.

The Second Randomized Trial - FK506/Prednisone vs. FK506/Azathioprine/ Prednisone

On the basis of these results, a prospective, randomized open label trial was begun in August, 1991, comparing two FK506-based regimens, with and without Azathioprine (Table 2).[12,13,20,21] This trial was limited to adults undergoing kidney transplantation alone who consented to enter the trial. Children, patients receiving multiple concomitant organs, and patients who refused, were excluded. The patient population was otherwise unselected, with 25% of the patients undergoing retransplantation, 13% having a panel reactive antibody of over 40%, and 18% of the patients being over the age of 60. Date on all 397 cases entered into the trial, which

ended December 9, 1993, were recently presented.[13] The overall 1 and 2 year actuarial patient survival was 95% and 93%, and the overall 1 and 2 year actuarial graft survival was 89% and 83%. (Table 3, Figure 1). No significant differences in patient or graft survival were seen between the double and triple drug regimens.

A multivariate analysis was performed to search for any factors predictive of graft survival. The only factor found was the presence or absence of early graft function. The 1 and 2 year actuarial graft survival for patients with immediate graft function was 94% and 89%; however, in patients with initial non-function (defined either as lack of urine output within the first 48 hours or the need for dialysis within the first week after transplantation), the 1 and 2 year actuarial graft survival was 78% and 71% (Figure 2 - $P < .0001$, relative risk 3.53, range 2.09-5.91). Other factors, such as the presence or absence of rejection, recipient age or race, antibody level, or primary/retransplant status, were not associated with differential outcomes (see Table 4).

The mean serum creatinine was 2.0 ± 1.1 mg/dl, and the calculated creatinine clearance was 56 ± 27 ml/min. The mean BUN was 32 ± 16 mg/dl. There was no difference between the two groups.

Triple therapy was associated with less rejection than double therapy, both in patients treated with steroids (44% versus 54%, $P < .05$), and in those requiring antilymphocyte therapy (7% versus 14%, $P < .04$). The incidence of other adverse events, such as early non-function, CMV, PTLD, and new onset diabetes, was not influenced by immunosuppressive group (Table 5).

Forty-nine percent of the successfully transplanted patients were weaned off

steroids. Thirty-five percent of the patients were off antihypertensive medications, and 39% were on 1 medication only. The mean serum cholesterol was 195 ± 49 mg./dl. There were no differences between the two groups in these parameters (Table 6).

There was a high incidence of cross-over, more from triple to double therapy (40%) than from double to triple therapy (17%).

This study concluded that FK-506 was an effective immunosuppressive agent in renal transplant patients, with excellent 1 and 2 year patient and graft survival, and an ability to wean steroids in nearly half and antihypertensive medications in over one-third of the patients. The benefit of Azathioprine was limited to a reduced incidence of rejection, but no benefit was seen in terms of patient or graft survival. Given the need to discontinue Azathioprine in 40% of the patients initially randomized to triple therapy, it was felt that Azathioprine as a third agent was of somewhat limited usefulness, and that perhaps one of the new Azathioprine substitutes, such as Mycophenolate Mofetil,[22] or Brequinar,[23] might be worth evaluating. In the interim, a new randomized trial of FK-506-based therapy was started, comparing FK-506/Prednisone with FK-506/Prednisone and a one week course of low-dose Cyclophosphamide. This trial is ongoing.

Pediatric Transplantation

Pediatric renal transplantation accounts for about 7% of the caseload in our institution. Given both the small number of cases and the nature of the patient population, a randomized trial was not possible in our pediatric patients. In addition, results with cyclosporine-based therapy in the pediatric patients were quite reasonable, with 100% and 97% one and four year actuarial patient survival and 100% and 85%

one and four year actuarial graft survival.[14,24] However, the ability to withdraw steroids seemed particularly important in children, and, by January, 1994, 43 cases had been performed under FK-506 therapy.[25] Thirty-five percent of these cases were retransplantations, many in children previously transplanted elsewhere. Twelve percent were in sensitized children. About half were with kidneys from living donors.

Results demonstrated 100% patient survival at one and three years (Table 7, Figure 3). The one and three year actuarial graft survival was 98% and 85%. The mean serum creatinine was 1.2 ± 0.6 mg/dl, and the calculated creatinine clearance was 75 ± 23 ml/min/1.73 m^2. The mean BUN was 26 ± 11 mg/dl.

Sixty-two percent of the children were weaned off steroids, and the associated effect on growth is shown in Table 8. Preadolescent children off steroids had the most dramatic changes and actually went beyond catch-up growth to become slightly taller than average.

The main adverse events are listed in Table 9. The most important complications were viral infections. CMV was seen in 6 (14%) children, 5 of whom were seronegative recipients of organs from seropositive donors. Intravenous gancyclovir was used successfully in all cases. EBV-associated PTLD was also seen in 5 (12%) cases; immunosuppression was temporarily withdrawn, and antiviral therapy with Gancyclovir or Acyclovir was initiated. In all cases, the PTLD resolved with good preservation of graft function. These complications probably represent a learning curve in the use of FK-506 in children, as no new cases of PTLD have been seen in patients transplanted during the past 21 months (as of October, 1994).

Rejection was seen in 58% of patients; 7% required antilymphocyte therapy.

All rejections were biopsy proven, and most occurred within the first two weeks after transplantation.

The pediatric data demonstrated that excellent results can be obtained with FK-506. In addition, the ability to wean steroids in a majority of children has led to significant improvements in growth.

Rescue

The first use of FK-506 in a renal transplant patient was in an attempt to rescue a chronically rejecting allograft. This attempt failed (the patient went on to receive a second kidney under FK506 immunosuppression, and it is functioning well 5 years later), as did the next 5 attempts at rescue. Most of these early efforts were in retrospect, poorly indicated, as the patients had a significant degree of scarring and/or chronic rejection. However, when rescue was attempted in patients with acute rejection who had failed conventional therapy, a number of allografts were salvaged. In both adults and children, 70-74% of patients were successfully rescued.[17,25,26] In patients with acute cellular rejection only, the success rate was 85%; in patients with both cellular and vascular rejection, the success rate was 65%, and in patients with acute cellular rejection and primary non-function of the allograft, the success rate was only 40% (Table 10). Seventy-nine percent of the patients had received one or more courses of antilymphocyte therapy prior to being referred for rescue. Eighty-three percent had been transplanted elsewhere. Twenty-three percent of the patients arrived on dialysis; half of them were successfully rescued. Twenty-one percent of successfully rescued patients were able to be weaned off Prednisone. Thus, FK-506 has been useful in salvaging the majority of the patients with refractory acute rejection

under conventional therapy.

Bone Marrow Augmentation

While this subsection has perhaps less to do specifically with FK-506, it discusses an area of increasing importance in our clinical program. This project began with the observation that patients with extremely long graft survival (27-29 years) were found to be micro-chimeric with respect to the donor.[27-30] Donor cells were found not only in the allograft but also in the peripheral blood, skin, and lymph nodes. On the basis of this observation, we postulated that infusion of donor bone marrow at the time of the transplant would augment chimerism in the recipient.[18] The first combined, simultaneous kidney/bone marrow transplantation was performed on December 14, 1992. An early report of the first 10 patients was presented in May, 1994, at the American Society of Transplant Surgeons.[18] By September 27, 1994, 30 kidney/bone marrow transplantations had been performed. In 6 cases, pancreatic islets were also infused, and in 4 cases, a pancreas transplant was also performed. Immunosuppression was with routine FK-506 and steroids; the pancreas recipients also received Azathioprine, 2 mg/kg/d. All patients, except one, were undergoing their first transplant. Radiation therapy, cytoreduction therapy, or induction antilymphocyte therapy was not given. Nineteen concurrent control patients, who did not receive bone marrow (usually because of refusal of the donor family to consent to vertebral body recovery), were also studied. Immunologic testing for chimerism was performed prior to transplantation and at regular intervals post-transplantation.

With a mean follow-up of 8.0 ± 6.4 months, all study patients are alive, and 28 (93%) have functioning renal allografts (Table 11). Two kidney/bone marrow patients

have lost their allografts at 16 months after transplantation, one to non-compliance and one to rejection. The mean serum creatinine is 1.8 ± 0.6 mg/dl, and the BUN is 30 ± 9 mg/dl. In the control patients, 18 (95%) patients are alive and 17 (89%) have functioning kidneys, with a mean serum creatinine of 2.3 ± 1.3 mg/dl and a BUN of 35 ± 14 mg/dl. The incidence of early non-function, rejection, and CMV was comparable between study and control patients and is shown in Table 11. Graft vs. host disease was not seen in any study or control patient.

The chimerism studies in the May, 1994, presentation suggested routine augmentation in all of the nine evaluable patients, as documented either by flow cytometry, PCR, or fluorescent in-situ hybridization (for Y-chromosome analysis). Chimerism was also seen in the control patients, but less often (3 or 5 evaluable patients) and to a lesser degree. Unpublished data on the larger group seems to be similar, although the analysis is still in progress.

The conclusions drawn thus far from the experience are that kidney/bone marrow transplantation is straightforward and safe to perform, that it is associated with routine augmentation of chimerism, that graft vs. host disease is not a problem, that excellent patient and graft survival are obtained, and that the early events after transplantation are not affected. More follow-up will be required to access the long-term outcome with bone marrow augmentation.

Toxicity

FK-506 has the same toxicities that have been seen with cyclosporine, namely nephrotoxicity, neurotoxicity, and diabetogenicity.[31-37] In general, these side effects are similar in degree and reversibility. The initial incidence of new onset diabetes has

been as high as 18%-20%;[13,37] however, much of this is reversible with reduction in both the FK-506 and the steroid dosage, and the final incidence of new onset insulin dependence, 6-10%, is about the same as that reported with cyclosporine.[38-40]

CONCLUSIONS

It is fair to say that FK-506 has dramatically changed the outcome of renal transplantation in our institution. As a program committed to transplanting relatively high-risk patients, we have previously reported 1 year actuarial graft survivals of 74-80%.[41-42] Our most recent data in adults have shown a 15% improvement in 1 and 2 year actuarial graft survival, as well as an ability to discontinue steroids in half of the patients. In pediatric patients, the use of FK-506 has enabled us to achieve the same good primary outcomes and for the first time allowed dramatic gains in height in the majority of patients weaned off prednisone. The ability to salvage over 70% of renal allografts failing conventional immunosuppression has also proved to be an important advantage. Finally, the development of bone marrow augmentation protocols has allowed the exploration of chimerism in renal transplant patients, and this may have important long-term implications. What FK-506 has not eliminated are the problems of acute rejection and the persistence of antibody-mediated events. In addition, the same fundamental toxicities seen with cyclosporine are present with FK-506; unfortunately, a T-cell active immunosuppressive agent without these side effects does not yet exist. For now, notwithstanding the problems noted above, it can be said that FK-506, in our hands, represents a significant step forward in immunosuppression for kidney transplant patients.

SUMMARY

1. In an unselected adult renal transplant population, FK-506 as the primary immunosuppressive agent has been associated with a one and two year actuarial patient survival of 95% and 93% and 1 and 2 year actuarial graft survival of 89% and 83%. Forty-nine percent of successfully transplanted patients have been weaned off steroids.
2. In pediatric renal transplant patients, FK-506 has been associated with 100% one and three year actuarial patient survival and 98% and 85% one and three year actuarial graft survival. 62% of successfully transplanted patients have been taken off prednisone, with dramatic improvements in height.
3. FK-506 has been successful in rescuing 70-74% of adult or pediatric renal transplant patients with acute rejection that has failed conventional therapy.
4. Kidney/bone marrow transplantation under FK-506 therapy has been successfully performed, without graft vs. host disease and with routine augmentation of chimerism.
5. The side effects of FK-506 include nephrotoxicity, neurotoxicity, and diabetogenicity; they are comparable to those seen with cyclosporine.
6. FK-506 is an important new addition to the immunosuppressive armamentarium in renal transplant patients.

FIGURE LEGENDS

Figure 1: Actuarial Patient and Graft Survival

Figure 2: Graft Survival in Patients With and Without Initial Graft Function

Figure 3: Pediatric Kidney Transplantation Under FK506 - Patient and Graft Survival

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fig 1

University of Pittsburgh - Kidney Transplantation 8/1/91 - 12/9/93
FK506/Prednisone vs FK506/Azathioprine/Prednisone

Actuarial Patient and Graft Survival

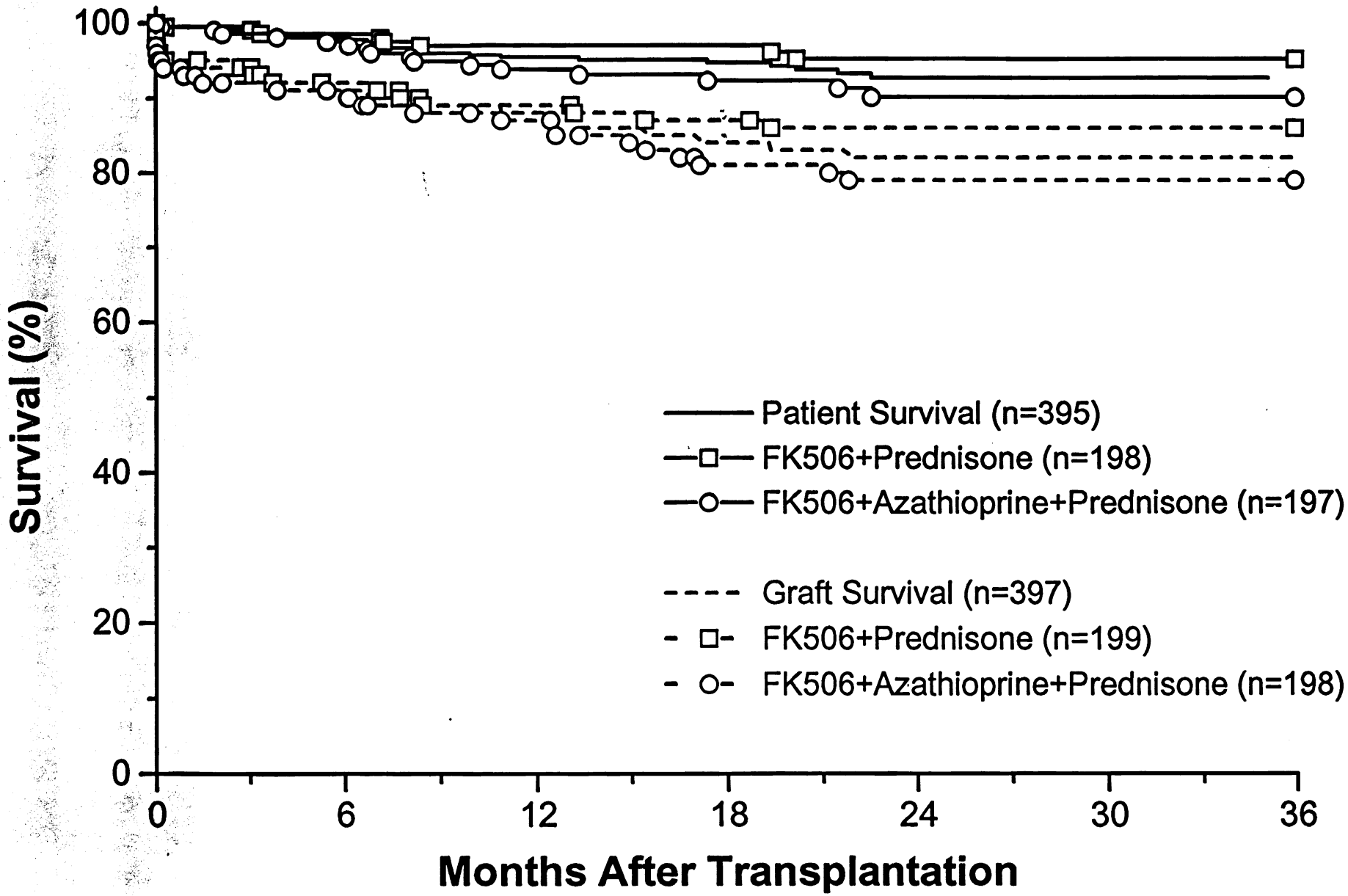

fig 2

University of Pittsburgh - Kidney Transplantation 8/1/91 - 12/9/93
FK506/Prednisone vs FK506/Azathioprine/Prednisone
ATN

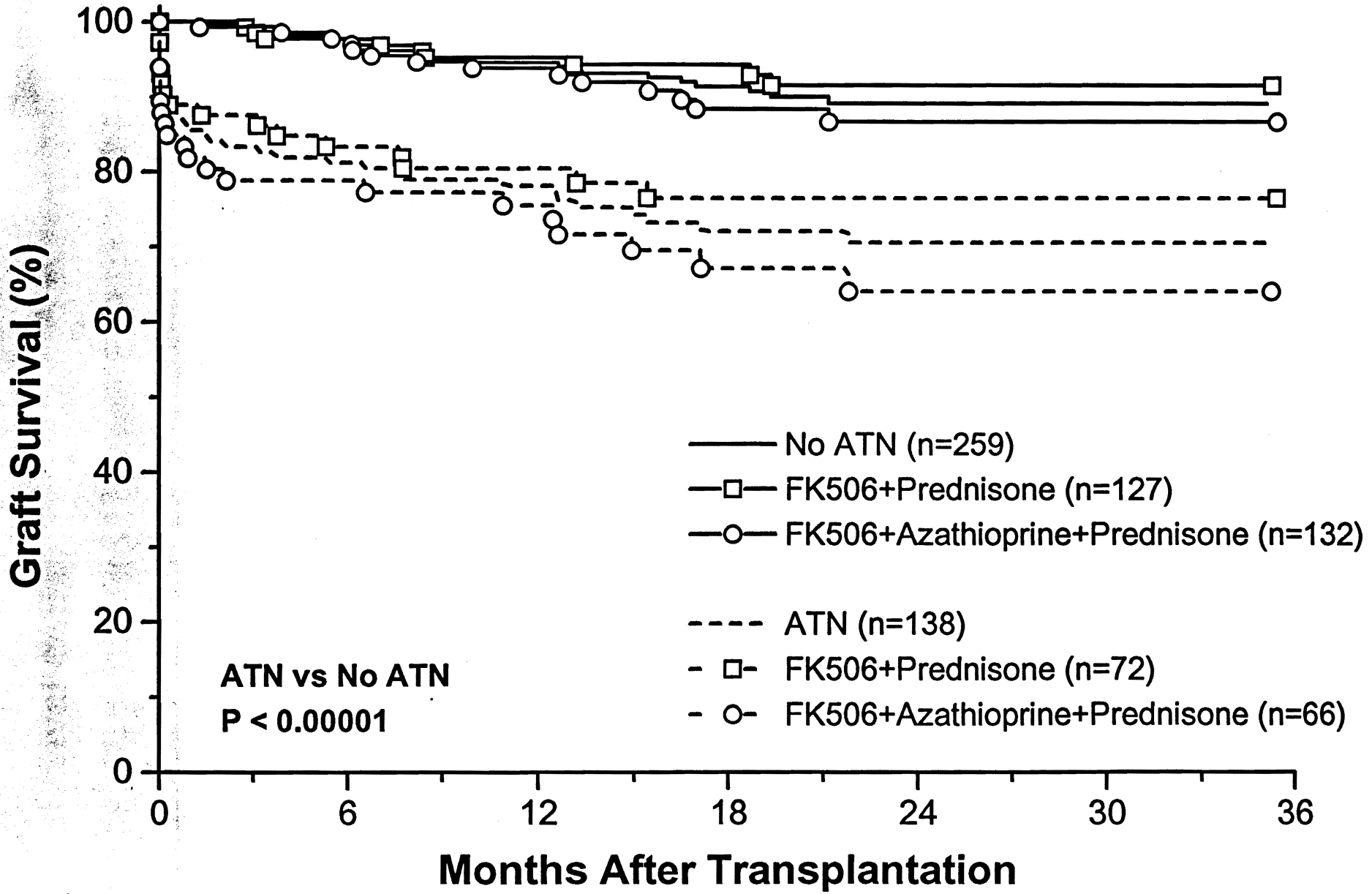

Fig 3

Pediatric Kidney Transplantation Under FK506

Patient and Graft Survival

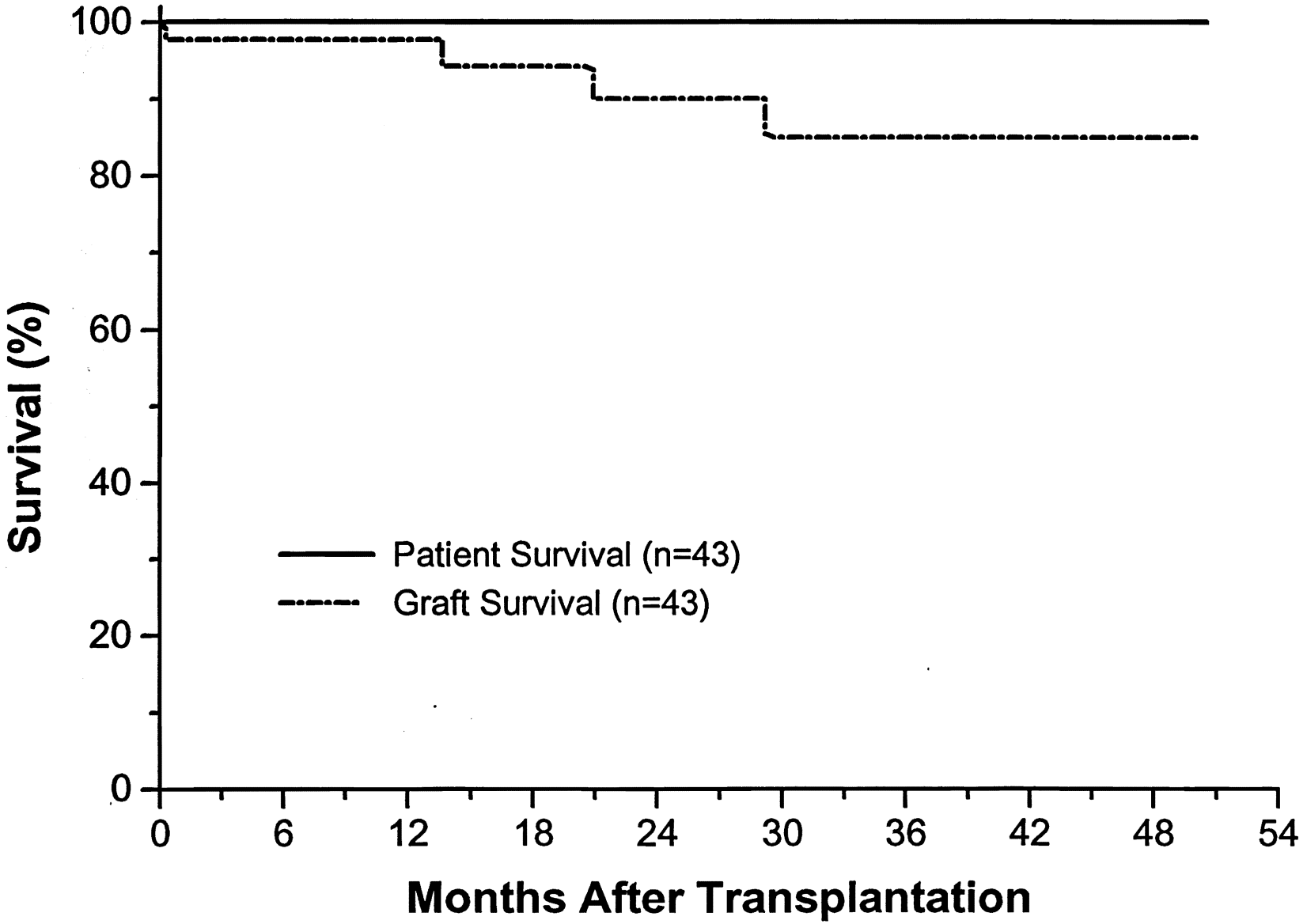

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TABLE 1

EARLY EXPERIENCE WITH FK506 IN RENAL TRANSPLANTATION

IMMUNOSUPPRESSION	FK506	CYCLOSPORINE
N	240	196
1 Yr. Actuarial Patient Survival 1 Yr. Actuarial Graft Survival	90% 74%	94% 77%
Off Steroids Off Anti-hypertensive Medications	44% 43%	0% 25%
Cholesterol (mg/dl)	187 ± 51	236 ± 59*

* $p < .0001$

TABLE 2

IMMUNOSUPPRESSIVE PROTOCOL - FK506/PREDNISONE VS. FK506/AZATHIOPRINE/PREDNISONE

IMMUNOSUPPRESSION

	FK506	STEROIDS	AZATHIOPRINE
Preop	0.15 mg/kg po	Methylprednisolone IV 1000 mg	3 mg/kg
Postop	0.1 mg/kg IV Continuous Infusion 0.15 mg/kg po bid when taking po	Methylprednisolone IV 50 mg IV q 6h x 4 doses 40 mg IV q 6h x 4 doses 30 mg IV q 6h x 4 doses 20 mg IV 6h x 4 doses 20 mg IV q 12h x 2 Prednisone 20 mg po qd	3 mg/kg/d

TABLE 3

FK506/PREDNISONE VS. FK506/AZATHIOPRINE/PREDNISONE - ACTUARIAL SURVIVAL

	FK506/Pred	FK506/Aza/Pred	Overall
N	199	198	397
Patient			
1 Yr.	97%	94%	95%
2 Yrs.	95%	90%	93%
Graft			
1 Yr.	90%	88%	89%
2 Yrs.	86%	79%	83%

p=ns

TABLE 4

FK506/PREDNISONE VS. FK506/AZATHIOPRINE/PREDNISONE SELECTED SUBGROUP ANALYSIS - ACTUARIAL GRAFT SURVIVAL (OVERALL RESULTS)

	1 Year	2 Years
First Cadaver	91%	82%
Retransplant	83%	80%
PRA > 40%	87%	85%
Recipient Age ≥ 60 yrs.	87%	75%
Black Recipient	88%	74%
No Rejection Rejection	91% 87%	86% 79%
*No ATN ATN	94% 78%	89% 71%

* $p < .0001$

TABLE 5

FK506/PREDNISONE VS. FK506/AZATHIOPRINE/PREDNISONE ADVERSE EVENTS

	FK506/PRED	FK506/AZA/PRED	OVERALL	
Rejection-Steroids	54%	44%	49%*	*p<.05
Rejection-OKT3/ATG	14%	7%	10%+	+p<0.04
ATN	36%	33%	35%	
CMV	15%	16%	16%	
PTLD	2%	1%	1%	
New Onset Diabetes	12%	9%	10%	

TABLE 6

FK506/PREDNISONE VS. FK506/AZATHIOPRINE/PREDNISONE

	FK506/PRED	FK506/AZA/PRED	OVERALL
Off Steroids	50%	49%	49%
Off Anti-hypertensive medications	37%	34%	35%
Serum Cholesterol (mg/dl)	192 ± 52	199 ± 45	195 ± 49

TABLE 7

PEDIATRIC KIDNEY TRANSPLANTATION UNDER FK506
ACTUARIAL SURVIVAL

N=43

	One Year	Three Years
Patient	100%	100%
Graft	98%	85%

TABLE 8

GROWTH AFTER PEDIATRIC KIDNEY TRANSPLANTATION UNDER FK506

Z-SCORE (± SD)

	ON STEROIDS		OFF STEROIDS	
	≤ 12 Years	> 12 Years	≤ 12 Years	> 12 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)

TABLE 9

PEDIATRIC KIDNEY TRANSPLANTATION UNDER FK506
ADVERSE EVENTS

Rejection - Steroids OKT3/ATG	58% 7%
CMV PTLD	14% 12%
ATN	7%
Temporary New Onset Diabetes (Resolved in all cases)	7%

TABLE 10

FK506 RESCUE THERAPY IN RENAL TRANSPLANTATION

N	77
Successful Rescue Overall	 74%
Acute Cellular Rejection Cellular + Vascular Rejection Cellular Rejection and 1^0 Non-function	85% 65% 40%
On Dialysis	50%
Off Steroids	21%

TABLE 11

	KIDNEY/BONE MARROW	CONTROL
N	30*	19
Patient Survival	100%	95%
Graft Survival	93%	89%
Graft vs. Host Disease	0%	0%
Rejection	73%+	58%
OKT3	13%	11%
ATN	17%	16%
CMV	13%	16%
Off Steroids	21%	22%

* Includes 6 kidney/islet/bone marrow
4 kidney/pancreas/bone marrow

\+ $p=0.26$