CHAPTER 21

Renal Transplantation at the University of Pittsburgh: The Impact of FK506

Ron Shapiro, Mark Jordan, Velma P. Scantlebury, Carlos Vivas, H. Albin Gritsch, Abdul S. Rao, Massimo Trucco, Adriana Zeevi, Anthony J. Demetris, Parmjeet Randhawa, Robert J. Corry, Francesca Egidi, Horacio Rilo, Camillo Ricordi, Patricia Carroll, Andreas Tzakis, Jerry McCauley, Demetrius Ellis, Nisan Gilboa, William Irish, Sandi Mitchell, John J. Fung, Thomas R. Hakala, Richard L. Simmons, and Thomas E. Starzl

University of Pittsburgh, School of Medicine
Pittsburgh Transplantation Institute
Pittsburgh, Pennsylvania

FK506 (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). FK506 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 also touch on our series of transplants with bone marrow augmentation (18). We hope to demonstrate that FK506 is an excellent immunosuppressive agent for patients undergoing renal transplantation and that it represents a formidable addition to our armamentarium.

Early Experience

The first 2 years' experience with FK506 in renal transplant patients included a pilot series, a small randomized trial comparing FK506 with CsA, and a larger group of patients not eligible for the randomized trial who were given the choice of receiving FK506 or not. 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 CsA-based immunosuppression (19). The patients in the randomized trial were also analyzed separately, with outcomes similar to the larger group. Comparable patient and graft survival rates were seen between FK506 and CsA-treated patients (Table 1). However, it was possible for over 40% of the patients on FK506 to be taken off prednisone, and antihypertensive medication requirements were lower in the FK506 group. In addition, serum cholesterol levels were significantly lower in the

Table 1. Early experience with FK506 in renal transplantation.

Immunosuppression	n=240 FK506	n=196 CsA
1-yr actuarial patient survival	90%	94%
1-yr actuarial graft survival	74%	77%
Off steroids	44%	0%
Off antihypertensive medications	43%	25%
Cholesterol (mg/dl)	187±51	236±59[a]

[a]p<0.0001

Clinical Transplants 1994, Terasaki and Cecka, Eds. UCLA Tissue Typing Laboratory, Los Angeles, California

Table 2. Immunosuppressive protocols- FK506/ prednisone versus 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	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	3 mg/kg/d
	0.15 mg/kg po bid when taking po	20 mg IV 6h x 4 doses 20 mg IV q 12h x 2 Prednisone 20 mg po qd	

Table 3. FK506/prednisone versus FK506/azathioprine/prednisone - actuarial survival.

	n=199 FK506/Pred (%)	n=198 FK506/Aza/Pred (%)	n=397 Overall (%)
Patient			
1-Yr	97	94	95
2-Yrs	95	90	93
Graft			
1-Yr	90	88	89
2-Yrs	86	79	83
p=NS			

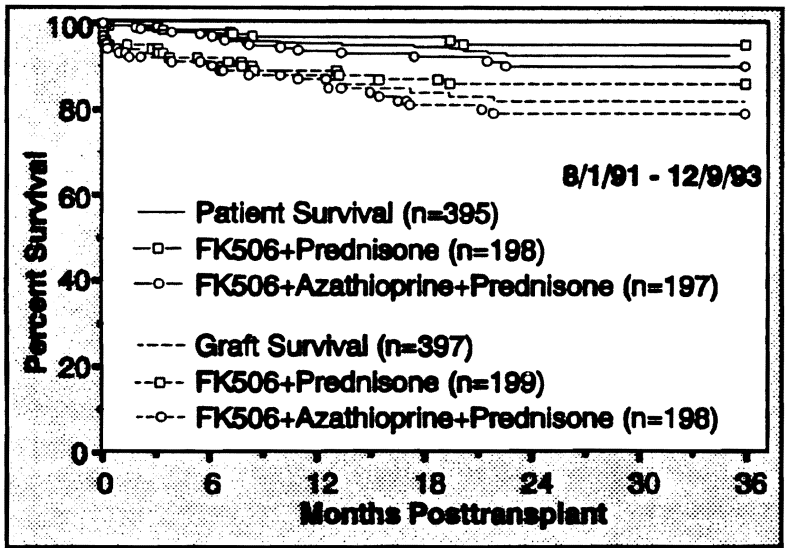

Figure 1. Actuarial patient and graft survival.

FK506-treated patients. The conclusion of this early work, during a time when the dosing and toxicities were still being evaluated, was that FK506 was certainly as effective as conventional therapy and might even have some advantages with regard to secondary issues.

The Second Randomized Trial - FK506/Prednisone versus FK506/Azathioprine/ Prednisone

On the basis of these early results, a prospective, randomized open-label trial was begun in August 1991, comparing 2 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% undergoing retransplantation, 13% with a panel-reactive antibody of over 40%, and 18% over age 60. Data on all 397 patients entered into the trial, which ended December 9, 1993, were recently presented (13). The overall 1- and 2-year actuarial patient survival rates were 95% and 93%, respectively, and the overall 1- and 2-year actuarial graft survival rates were 89% and 83%, respectively (Table 3, Fig. 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 significant factor identified was the presence or absence of early graft function. The 1- and 2-year actuarial graft survival rates for patients with immediate graft function were 94% and 89%, respectively. However, in patients with initial nonfunction (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 rates were 78% and 71%, respectively (Fig. 2 - $p<0.0001$, relative risk 3.53, range 2.09-5.91). Other factors, such as the pres-

ence or absence of rejection, recipient age or race, antibody level, or primary/retransplant status, were not associated with differential outcomes (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 2 groups.

Triple therapy was associated with less rejection than double therapy, both in patients treated with steroids (44% vs 54%, p<0.05) and in those requiring antilymphocyte therapy (7% vs 14%, p<0.04). The incidence of other adverse events, such as early nonfunction, CMV, posttransplant lymphoproliferative disorder (PTLD), and new-onset diabetes, was not influenced by the immunosuppressive group (Table 5).

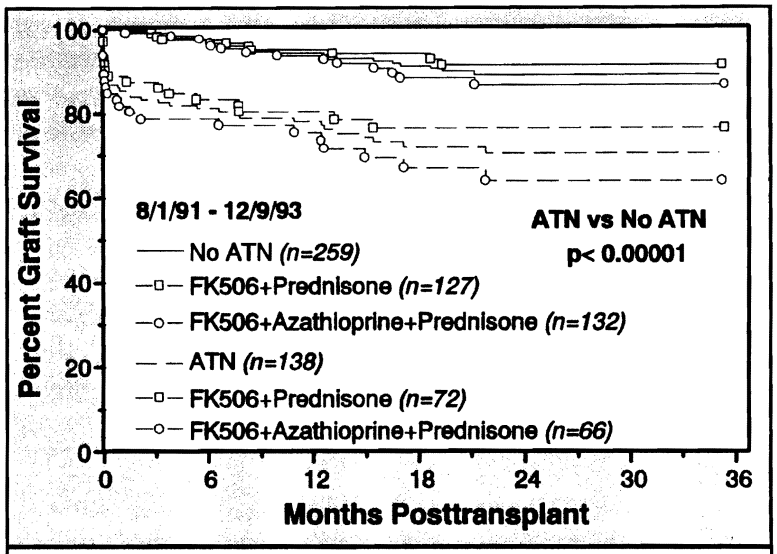

Figure 2. Graft survival in patients with and without initial graft function.

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 one medication only. The mean serum cholesterol was 195±49 mg/dl. There were no differences between the 2 groups with respect to these parameters (Table 6).

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

This study showed that FK506 was an effective immunosuppressive agent in renal transplant patients. The 1- and 2-year patient and graft survival rates were excellent. It was possible 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. 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

Table 4. FK506/prednisone versus FK506/azathioprine/prednisone selected subgroup analysis - actuarial graft survival (overall results).

	n=397 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	91	86
Rejection	87	79
No ATN[a]	94	89
ATN	78	71

[a]p<0.0001

Table 5. FK506/prednisone versus FK506/azathioprine/prednisone adverse events.

	n=199 FK506/Pred (%)	n=198 FK506/Aza/Pred (%)	n=397 Overall (%)
Rejection-steroids	54	44	49[a]
Rejection-OKT3/ATG	14	7	10[b]
ATN	36	33	35
CMV	15	16	16
PTLD	2	1	1
New-onset diabetes	12	9	10

[a]p<0.05, [b]p<0.04

Table 6. FK506/prednisone versus FK506/azathioprine/prednisone.

	n=199 FK506/Pred	n=198 FK506/Aza/Pred	n=397 Overall
Off steroids	50%	49%	49%
Off antihypertensive medications	37%	34%	35%
Serum cholesterol (mg/dl)	192±52	199±45	195±49

Only for functioning kidneys

be worth evaluating. In the interim, a new ongoing randomized trial of FK506-based therapy was started, comparing FK506/prednisone with FK506/prednisone and a one-week course of low-dose cyclophosphamide.

Pediatric Transplantation

Pediatric renal transplantation accounts for about 7% of the caseload at our institution. Because of 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 CsA-based therapy in the pediatric patients were quite reasonable, with 100% and 97% 1- and 4-year actuarial patient survival rates, respectively, and 100% and 85% one- and 4-year actuarial graft survival rates, respectively (14,24). However, steroid withdrawal seemed particularly important in children, and, by January 1994, 43 cases had been performed under FK506 therapy (25). Thirty-five percent of these cases were retransplantations, many in children previously transplanted elsewhere. Twelve percent were in sensitized children. About half involved kidneys from living donors.

Results demonstrated 100% patient survival at one and 3 years (Table 7, Fig. 3). The one- and 3-year actuarial graft survival rates were 98% and 85%, respectively. The mean serum creatinine was 1.2±0.6 mg/dl, and the calculated creatinine clearance was 75±23 ml/min/1.73 m². 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 taken off steroids showed 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 ganciclovir was used successfully in all cases. EBV-associated PTLD was also seen in 5 (12%) cases. Immunosuppression was temporarily withdrawn, and antiviral therapy with ganciclovir 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 FK506 in children, as no new cases of PTLD have been seen in patients transplanted during the past 21 months (as of October 1994).

Table 7. Pediatric kidney transplantation under FK506 actuarial survival.

	n=43 1 Year	3 Years
Patient	100%	100%
Graft	98%	85%

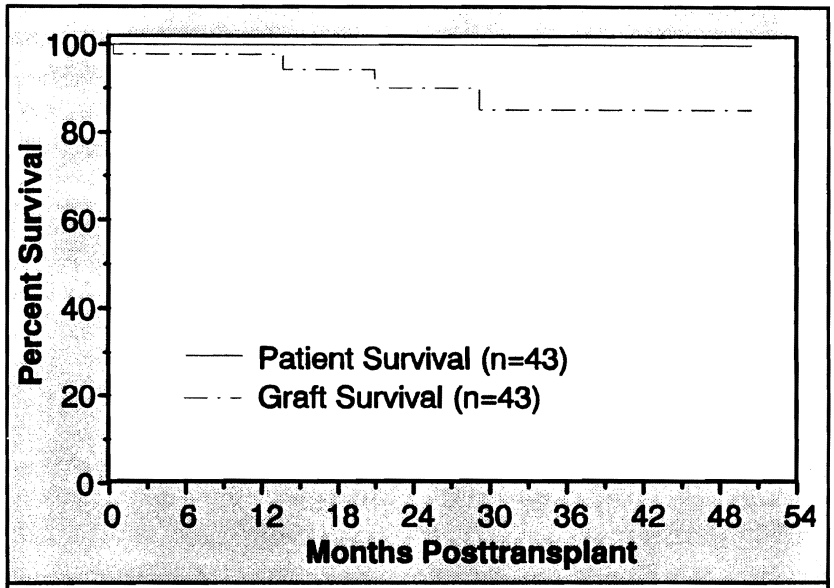

Figure 3. Pediatric kidney transplantation under FK506 - patient and graft survival.

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)

Rejection occurred in 58% of patients; 7% required antilymphocyte therapy. All rejections were biopsy proven, and most occurred within the first 2 weeks after transplantation.

The pediatric data demonstrated that excellent results can be obtained with FK506. In addition, the ability to wean the majority of children off of steroids has led to significant improvements in growth.

Rescue

The first use of FK506 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, which is still functioning well after 5 years), as did the next 5 attempts at rescue. Most of these early efforts were, in retrospect, poorly indicated, since 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 CsA-based 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 nonfunction 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, and half of them were successfully rescued. Twenty-one percent of successfully rescued patients were weaned off prednisone. Thus, FK506 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 FK506, it addresses an area of increasing importance in our clinical program. This project began with the observation that patients with extremely long graft survival (27-29 yrs) were found to be micro-chimeric with

Table 9. Pediatric kidney transplantation under FK506 adverse events.

n=43	%
Rejection-Steroids	58
OKT3/ATG	7
CMV	14
PTLD	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	85
Cellular + vascular rejection	65
Cellular rejection and 1° nonfunction	40
On dialysis	50
Off steroids	21

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. Based on 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 FK506 and steroids. The pancreas recipients also received azathioprine, 2 mg/kg/day. All patients, except one, were undergoing their first transplantation. Radiation therapy, cytoreduction therapy, and induction antilymphocyte therapy were not given. Nineteen concurrent control patients, who did not receive bone marrow (usually because of refusal of the donor's family to consent to vertebral body recovery), were also studied. Immunologic testing for chimerism was performed prior to transplantation and at regular intervals posttransplantation.

With a mean follow-up of 8.0±6.4 months, all study patients were alive, and 28 (93%) had functioning renal allografts (Table 11). Two kidney/bone marrow patients lost their allografts at 16 months after transplantation, one to noncompliance and one to rejection. The mean serum creatinine was 1.8±0.6 mg/dl, and the BUN was 30±9 mg/dl. In the control patients, 18 (95%) patients were alive and 17 (89%) had 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 nonfunction, rejection, and CMV was comparable between study and control patients as shown in Table 11. Graft-versus-host disease was not seen in any study or control patient.

The chimerism studies presented in May 1994 suggested routine augmentation in all of the 9 evaluable patients, as documented either by flow cytometry, PCR, or fluorescent in-situ hybridization (for Y-chromosome analysis). Chimerism was also noted in the control patients, but less often (3 or 5 evaluable patients) and to a lesser degree. Unpublished data on the larger group is similar, although the analysis is still in progress.

The conclusions drawn thus far from this experience are that kidney/bone marrow transplantation is straightforward and safe to perform, that it is associated with routine augmentation of chimerism, that it is not accompanied by graft-versus-host disease, that it yields excellent patient and graft survival rates, and that it does not effect the early events after transplantation. More follow-up data will be required to assess the long-term outcome with bone marrow augmentation.

Toxicity

FK506 has the same toxicities that have been reported with CsA, 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 FK506 and steroid dosages. The final incidence of new-onset insulin dependence, 6-10%, is about the same as that reported with CsA (38-40).

CONCLUSIONS

It is fair to say that FK506 has dramatically changed the outcome of renal transplantation at our institution. As a program committed to transplanting relatively high-risk patients, we have previously reported one-year ac-

Table 11. Combined kidney/bone marrow transplantation.

	Kidney/Bone Marrow n=30[a] %	Control n=19 %
Patient survival	100	95
Graft survival	93	89
Graft-vs-host disease	0	0
Rejection	73[b]	58
OKT3	13	11
ATN	17	16
CMV	13	16
Off steroids	21	22

[a]includes 6 kidney/islet/bone marrow
4 kidney/pancreas/bone marrow
[b]p=0.26

tuarial graft survival rates of 74-80% (41,42). Our most recent data for adults have shown a 15% improvement in one- 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 FK506 has enabled us to achieve the same good primary outcomes and for the first time has 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, which may have important long-term implications. What FK506 has not eliminated are the problems of acute rejection and the persistence of antibody-mediated events. In addition, the same fundamental toxicities seen with CsA are present with FK506. Unfortunately, a T-cell-active immunosuppressive agent without these side effects does not yet exist. Notwithstanding the problems noted above, in our hands FK506 represents a significant step forward in immunosuppression for kidney transplant patients.

SUMMARY

1. In an unselected adult renal transplant population, FK506 as the primary immunosuppressive agent yielded one- and 2-year actuarial patient survival rates of 95% and 93% and one- and 2-year actuarial graft survival rates of 89% and 83%, respectively. Forty-nine percent of successfully transplanted patients were weaned off steroids.
2. In pediatric renal transplant patients, FK506 has been associated with 100% one- and 3-year actuarial patient survival rates and 98% and 85% one- and 3-year actuarial graft survival rates, respectively. Sixty-two percent of successfully transplanted patients were taken off prednisone, with dramatic improvements in height.
3. FK506 has been used successfully in rescuing 70-74% of adult or pediatric renal transplant patients with an acute rejection that failed conventional therapy.
4. Kidney/bone marrow transplantation under FK506 therapy has been successfully performed without graft-versus-host disease and with routine augmentation of chimerism.
5. The side effects of FK506 included nephrotoxicity, neurotoxicity, and diabetogenicity; they were comparable to those seen with CsA.
6. FK506 is an important new addition to the immunosuppressive armamentarium in renal transplant patients.

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