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## FK 506 in Clinical Kidney Transplantation

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Early reports on the use of FK 506 after kidney transplantation emphasized the ability to stop prednisone in a significant percentage of successfully transplanted patients.<sup>1,2</sup> In addition, there was a relative freedom from antihypertensive agents and a tendency toward low serum cholesterol levels. This report will summarize our experience to date with FK 506 in renal transplantation and will compare the results with a nearly concurrent group of patients treated with cyclosporine (CyA)-based immunosuppression.

### MATERIALS AND METHODS

Between March 27, 1989, the date of the first kidney transplant under FK 506 immunosuppression, and May 1, 1991, 464 kidney transplantations were performed at the University of Pittsburgh. Of these 28 were in patients who had received concomitant or previous liver transplants, and these were the only exclusions from the analysis. Of the 436 transplants in 425 patients, 196 received CyA-based immunosuppression; over 80% of this group received azathioprine as well (Table 1). Some 240 cases were treated with FK 506 and steroids. The mean recipient age was  $39.5 \pm 14.9$  years; 44 (10.1%) of the cases were performed in patients over 60 years of age, and 31 (7.1%) of the transplants were to children. Sixty (13.7%) of the cases involved black recipients. There was a significantly higher incidence of retransplantation in the FK 506 group—over 30% of the FK 506 cases were to patients undergoing their second to fifth transplant, whereas just under 20% of the CyA cases were retransplants ( $P < .005$ ). Over 25% of the transplants were to sensitized recipients. A higher percentage of living-donor cases were done under CyA—14.3% vs 5% of the FK 506 cases ( $P < .02$ ).

The mean donor age was  $34.0 \pm 16.6$  years; 73 (18.4%) of the cadaver transplants were with pediatric en bloc kidneys. The mean cold ischemia time was  $36.3 \pm 10.6$  hours. HLA matches and mismatches revealed a small number of good matches, with less than 2% of cases being 6-antigen matches and nearly two-thirds of cases having a 2-antigen match or less.

There was thus no attempt to be particularly discriminating in either donor or recipient selection. The FK 506 cases were actually a higher-risk group than was the CyA group—more retransplants, fewer living donor cases, slightly more sensitized patients, and en bloc kidneys. This had the effect of subjecting FK 506 to a rather stringent evaluation.

FK 506 dosage has evolved toward decreasing amounts. From March 1989 until June 1990, 0.075 mg/kg was infused intravenously over 4 hours twice a day. From June 1990 until August 1990, 0.15 mg/kg per day was given as a continuous infusion over 24 hours. Since August 1990, a continuous intravenous infusion of 0.1 mg/kg per day has been used until

patients are on a solid diet, at which point an oral dose of 0.15 mg/kg BID is started. A steroid bolus followed by a short recycle was used in most cases. CyA-based regimens varied slightly in the details but generally did not involve sequential therapy.

## RESULTS

The median follow-up is 1.12 years, with a range of 0.17 to 2.25 years. Overall 1-year actuarial patient survival is 92%, with 94% in the CyA group and 90% in the FK 506 group (Table 2); 8.2% of the patients have died; the percentages in the CyA and FK 506 groups are identical, and the causes of death have been similar.

One-year actuarial graft survival for all cases is 76%, with 77% in the CyA group and 74% in the FK 506 group. Graft survival was not significantly different between CyA and FK 506. This held true in adults, children, blacks, whites, first transplants, retransplants, low PRA patients, high PRA patients, cadaveric, and living-donor patients.

The ATN rate was similar for both groups and was 38.4% in cadaveric transplant recipients.

The incidence of rejection was 57% and 59%, respectively, in the CyA and FK 506 groups. Twenty-one percent of the CyA group required OKT3 for steroid-resistant rejection, while 19% of the FK 506 group required OKT3. The incidence of CMV was 15.3% and 17.5%, respectively, in the two groups.

Mean serum creatinine in the CyA and FK 506 groups was  $1.9 \pm 1.7$  mg/dL and  $2.1 \pm 1.2$  mg/dL, respectively (Table 2). Mean BUN was  $31 \pm 17$  mg/dL and  $36 \pm 22$  mg/dL, respectively. Mean uric acid was  $7.2 \pm 2.6$  mg/dL in the CyA group and  $8.1 \pm 2.4$  mg/dL in the FK 506 group.

The chief differences were found in the prednisone dosages. Forty-four percent of patients on FK 506 who had functioning kidneys were taken off prednisone completely, whereas all of the CyA patients required chronic prednisone therapy (Tables 3 and 4). Additionally, 43% of patients were off antihypertensive agents in the FK 506 group as opposed to 25% of patients in the CyA group.

Mean serum cholesterol was  $187 \pm 51$  mg/dL in the FK 506 group and  $236 \pm 59$  mg/dL in the CyA group ( $P < .0001$ ) (Table 2).

Within this large group of patients was a small group of 57 good-risk patients who were entered into a randomized trial comparing CyA and FK 506 (Table 5). Patient and graft survival were similar, with 89% and 96% 1-year patient survival and 79% and 82% 1-year graft survival in the CyA and FK 506 groups, respectively (Table 6). However, 9 (31%) of the 29 CyA patients required conversion to FK 506.

In the randomized trial, the mean serum creatinine was  $1.8 \pm 0.7$  mg/dL in the CyA group and  $1.8 \pm 0.5$  mg/dL in the FK 506 group (Table 6). Mean BUN was  $29 \pm 11$  mg/dL and  $28 \pm 8$  mg/dL; uric acid was  $6.9 \pm 2.1$  mg/dL and  $7.4 \pm 2.2$  mg/dL, respectively, in the CyA and FK 506 groups. Serum cholesterol was  $183 \pm 39$  mg/dL in the FK 506 group and  $234 \pm 52$  mg/dL in the CyA group ( $P < .002$ ).

Of the FK 506 patients, 55% were off prednisone, while all of the CyA patients were on some dose of steroids (Tables 7 and 8). Forty-four percent of the FK 506 patients were off antihypertensive medications compared to 22% of CyA patients.

## DISCUSSION

The side effects of FK 506 are similar to those associated with CyA and include nephrotoxicity, neurotoxicity, and diabetogenicity. Nephrotoxicity is unquestionably a real issue in renal transplantation under FK 506; it is reversible with dosage reduction, although there is a component that may not be reversible. Neurotoxicity is manifested principally by tremors, paresthesias of the extremities, and insomnia. In general, the neurologic side effects were reversible with dosage reduction, and in some cases served as a marker for the need to make downward adjustments in FK 506 dosage.

The diabetogenicity issue is discussed elsewhere<sup>3</sup>; in brief, there is evidence that FK 506 is diabetogenic in about 15% to 20% of patients and is reversible in most cases. This is similar to the experience described with CyA.<sup>4</sup>

Despite these side effects there is no question that FK 506 has enormous potential advantages in renal transplantation. Both patient and graft survival are comparable to what can be achieved with conventional immunosuppression. However, the ability to discontinue steroids and antihypertensive agents and the lower serum cholesterol levels are important long-term considerations.

A still unanswered question is how best to use FK 506 in kidney transplantation. We have just begun a randomized trial comparing FK 506 and steroids with FK 506, azathioprine, and steroids, with the goal of reducing the incidence of both nephrotoxicity and rejection, while at the same time preserving the advantages associated with FK 506. In the future, we will be interested in looking at the combination of FK 506 with some of the newer agents that are being developed, such as bredinin, RS-61443, and mycophenolic acid.

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**Table 1**

## Recipient and Donor Characteristics

	CyA	FK 506	Total
No. Patients	191	234	425
No. Transplants	196	240	436
Mean age	38.2 ± 15.0 y	40.5 ± 14.7 y	39.5 ± 14.9 y
Pediatric cases	17 (8.7%)	14 (5.8%)	31 (7.1%)
Recipient age >60 y	15 (7.7%)	29 (12.1%)	44 (10.1%)
Black recipients	34 (17.3%)	26 (10.8%)	60 (13.7%)
* Retransplantation	38 (19.4%)	76 (31.7%)	114 (26.1%)
PRA >10%	45 (22.0%)	68 (28.0%)	113 (26.0%)
PRA >40%	26 (13.0%)	41 (17.0%)	67 (15.4%)
Cadaver	168 (85.7%)	228 (95.0%)	396 (90.8%)
† Living donor	28 (14.3%)	12 (5.0%)	40 (9.2%)
Donor age	32.9 ± 16.4 y	34.8 ± 16.7 y	34.0 ± 16.6 y
Cold ischemia time	37.0 ± 11.2 h	35.9 ± 10.1 h	36.3 ± 10.6 h
Pediatric en bloc	28 (16.7%)	45 (19.7%)	73 (18.4%)

\*  $P < .005$ .†  $P < .02$ .

**Table 2**

## Actuarial One-Year Survival

	CyA	FK506	Total
Patient survival			
All	94%	90%	92%
Graft survival			
All	77%	74%	76%
Cadaveric	75%	73%	74%
Living donor	89%	100%	96%
Creatinine	1.9 ± 1.7mg/dL	2.1 ± 1.2 mg/dL	
BUN	31.0 ± 17 mg/dL	36.0 ± 22 mg/dL	
Uric Acid	7.2 ± 2.6 mg/dL	8.1 ± 2.4 mg/dL	
* Cholesterol	236 ± 59 mg/dL	187 ± 51 mg/dL	

\*  $P < .0001$ ; all others  $P = NS$ .

**Table 3**

Contrasting Steroid Requirements in CyA and FK 506 Recipients

Prednisone Dose (mg/d)	CyA	FK 506
0	0 (0%)	78 (44%)
2.5–5.0	29 (22%)	42 (24%)
7.5–10.0	90 (68%)	45 (25%)
12.5–15.0	8 (6%)	9 (5%)
17.5–20.0	5 (4%)	3 (2%)

**Table 4**

## Antihypertensive Medications

No. Medications	CyA	FK 506
0	33 (25%)	76 (43%)
1	44 (33%)	58 (32%)
2	35 (27%)	35 (20%)
3	20 (15%)	8 (5%)

**Table 5**

Inclusion Criteria: Age Range 16–60; First Transplant; PRA<40%; No Hepatic Dysfunction; No Cardiac Disease

	CyA	FK506	Total
No. Patients	29	28	57
Mean age	39.4 ± 9.9 y	36.5 ± 11.6 y	38.0 ± 15.6 y
Donor age	36.3 ± 14.9 y	33.3 ± 17.1 y	35.1 ± 15.6 y
Cold ischemia time	33.2 ± 9.2 h	33.8 ± 8.2 h	33.5 ± 8.6 h
* Pediatric en bloc	4 (13.8%)	12 (42.9%)	16 (28.1%)

\*  $P = .0232$ .



**Table 6**

## Actuarial One-Year Survival

	CyA	FK506	Total
Patient survival	89%	96%	93%
Graft survival	79%	82%	80%
Creatinine	1.8 ± 0.7 mg/dL	1.8 ± 0.5 mg/dL	
BUN	29 ± 10 mg/dL	28 ± 8 mg/dL	
Uric acid	6.9 ± 2.1 mg/dL	7.4 ± 2.2 mg/dL	
* Cholesterol	234 ± 52 mg/dL	183 ± 39 mg/dL	

\*  $P < .0001$ ; all others  $P = NS$ .

**Table 7**

## Steroid Requirements

<b>Prednisone Dose (mg/d)</b>	<b>CyA</b>	<b>FK 506</b>
0	0 (0%)	15 (56%)
2.5–5.0	1 (6%)	3 (11%)
7.5–10.0	8 (44%)	6 (22%)
12.5–15.0	7 (39%)	1 (4%)
17.5–20.0	2 (11%)	2 (7%)

**Table 8**

## Antihypertensive Medications

No. Medications	CyA	FK 506
0	4 (22%)	12 (44%)
1	7 (39%)	7 (26%)
2	3 (17%)	5 (19%)
3	4 (22%)	3 (11%)