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Low-dose tacrolimus (FK506)-based immunosuppressive protocol in living donor renal transplantation

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Abstract In order to avoid the side effects of tacrolimus (FK506), a low-dose FK506-based regimen was started from 1 June 1991. The dose was adjusted to maintain the FK506 whole blood trough level at 15–20 ng/ml for 7 days postoperatively, at 10–15 ng/ml for 2 months, and under 10 ng/ml thereafter. The graft survival rates at 3 years and 5 years were 87.8 and 82.3 % (FK506) vs 86.8 and 86.8 % [cyclosporine (CyA)]. The incidence of acute rejection within the first 90 days was 31.6 % in the FK506 group which was lower than the 57.1 % of the CyA group ($P = 0.0585$). Grades of acute rejection episodes over IIA in the FK506 group were 20 %, which was lower than the 37 % in the CyA group. The mean oral dosages of FK506 were 0.061 and 0.04 mg/kg per day at 3 and 5 years, respectively. The incidence of new onset diabetes was 27.8 % in the FK506 group and 17.1 % in the CyA group. However, insulin therapy was withdrawn in all patients of the FK506 group within 5 months. The percentage of patients who required an antihypertensive agent was 28.6 % and 40 % in the FK506 group and 73.2 % and 88 % in the CyA group at 1 and 3 years, respectively ($P < 0.05$). Nephrotoxicity was seen in 20 % of the FK506 group and 14.3 % of the CyA group. Hypercholesterolemia was less frequent in the FK506 group than the CyA group. The FK506-based regimen described here is a protocol with the potential to reduce its adverse effects. The whole blood concentration of FK506 should be monitored and blood levels maintained in the range of 5–10 ng/ml after 90 postoperative days for optimal efficacy and minimal toxicity.

Key words Tacrolimus · FK506 · Renal transplantation · Low-dose

Introduction

Tacrolismus (FK506) has potent immunosuppressive activity in vitro and in experimental organ allografts [1, 2]. The mechanism of immunosuppression for FK506 and cyclosporine (CyA) has been reported to be similar. Early results with kidney transplantation have shown that FK506 is a promising agent for the prevention of allograft rejection and prolonging graft survival [3, 4]. Previous reports suggest that the use of FK506 resulted in equivalent patient and graft survival when compared with CyA-based regimens [5]. The side effects of FK506 are similar to those associated with CyA and include nephrotoxicity [6, 7], neurotoxicity [8], and diabetes [9]. These side effects are dose related and largely reversible with dose reduction. In order to avoid the side effects of FK506, we compared a low-dose FK506-based regimen with a CyA-based regimen in patients under going living donor renal transplantation.

Fig. 1 Graft survival rates

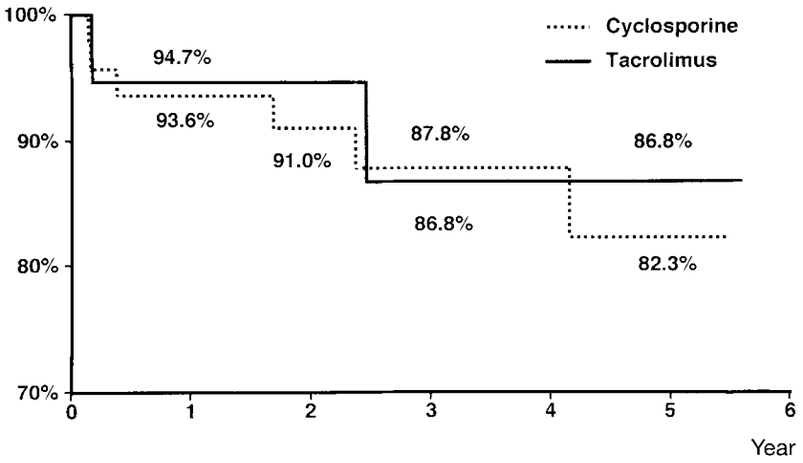

Table 1 Incidence and histological grading of acute rejection within first 3 months (*MP* Methylprednisolone pulses, *OKT3* orthodone OKT3 monoclonal antibodies, *ALG* antilymphocyte globulin, *ATG* antithymocyte globulin, *DSPG*)

		Cyclosporine	Tacrolismus	*P*
Frequency of rejection		28/49 (57.1%)	6/19 (31.6%)	0.0585
Number of rejections		47	9	
Steroid-resistant rejection		16/49 (32.7%)	4/19 (21.1%)	0.338
Treatment	MP	20 (42.6%)	4 (44.4%)	
	OKT3	11 (23.4%)	1 (11.1%)	
	ALG or ATG	3 (6.4%)	2 (22.2%)	
	DSPG	11 (23.4%)	1 (11.1%)	
	No therapy	2 (4.3%)	1 (11.1%)	
Banff histological grading				
B		6 (22.2%)	2 (22.2%)	
1		11 (40.7%)	5 (55.6%)	
2A		9 (33.3%)	2 (22.2%)	
2B		0	0	
3		1 (3.7%)	0	

Materials and methods

Nineteen living donor renal transplantations at our institution were performed using FK506 as the primary immunosuppressant between June 1991 and November 1996. The results of transplantation were compared to the outcomes of 49 living donor renal transplantations who received CyA-based immunosuppression. ABO incompatible transplantations were excluded.

FK506 was started 2 days preoperatively at the oral dose of 0.1–0.15 mg/kg twice daily. From transplant day 0 to day 3, a dose of 0.06–0.1 mg/kg per day of FK506 was administered initially as a continuous infusion for 24 h, followed by an oral dose of 0.1–0.15 mg/kg twice a day. The dose was adjusted to maintain a whole blood FK506 trough level of 15–20 ng/ml for 7 days postoperatively, 10–15 ng/ml for the following 2 months, and less than 10 ng/ml thereafter. Baseline immunosuppression was double-drug therapy, triple-drug therapy or quadruple-drug therapy. Double-drug therapy consisted of FK506 and prednisolone (Pred). Triple-drug therapy consisted of CyA with an initial oral dose of 6 mg/kg per day and then adjusted according to the trough blood level, mizoribine 2.5 mg/kg per day, and Pred. Quadruple-drug therapy consisted of CyA with an initial oral dose of 6 mg/kg per day (or FK506 with an initial oral dose of 0.06–0.1 mg/kg per day), mizoribine, Pred, and antilymphocyte globulin (ALG; 20–30 mg/kg per day for 10–14 days).

Blood concentrations of FK506 were measured by the double sandwich ELISA technique. A diagnosis of rejection was based primarily on the clinical findings: an increase in the serum creatinine or blood urea nitrogen concentration, or a decrease in the urine output. Graft biopsy was performed in most cases to confirm a diagnosis of rejection. Rejection was treated with 1–3 intravenous infusions of methylprednisolone (MP) pulses at a dose rate of 0.25 or 0.5 g. Steroid-resistant rejection was treated with ALG or orthoclone OKT3 monoclonal antibodies. Actuarial survival curves were calculated according to the Kaplan-Meier procedure. Statistical analysis was performed by considering the fixed end points using Student's *t*-test.

Results

There were no statistical differences in donor relationship, HLA matching, recipient age and sex, and

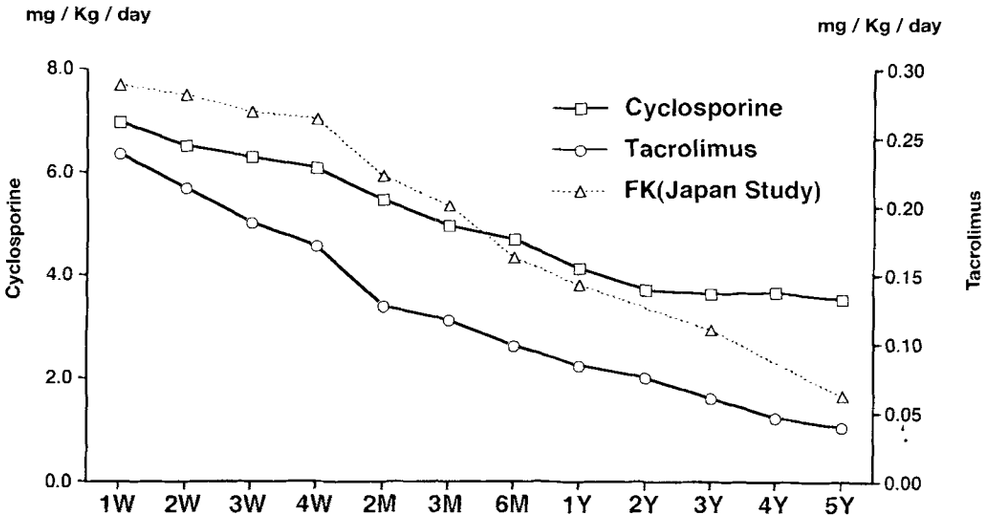

Fig. 2 Treatment dose of tacrolimus and cyclosporine. *W* Week, *M* month, *Y* year

Table 2 Incidence and timing of rejection

Time (weeks)	Cyclosporine	Tacrolismus	*P*
0–4	26 (53.1%)	5 (26.3%)	0.0469
4–12	14 (28.6%)	3 (15.8%)	0.2747
13–24	7 (14.9%)	3 (16.7%)	0.8593

Table 3 Percentage of patients requiring an antihypertensive agent in the tacrolismus group and in the cyclosporine group

Time post-transplantation [weeks (w), months (m), years (y)]	Cyclosporine		Tacrolismus		*P*
Pre	25/44	56.8%	8/15	53.3%	0.8146
1 w	36/48	75%	11/19	57.9%	0.1752
2 w	37/48	77.1%	12/19	63.2%	0.2551
3 w	38/48	79.2%	12/19	63.2%	0.1844
4 w	38/47	80.9%	12/19	63.2%	0.1386
2 m	35/46	76.1%	9/18	50%	0.0472
3 m	33/44	75%	7/18	38.9%	0.0077
6 m	32/44	72.7%	6/18	33.3%	0.004
1 y	30/41	73.2%	4/14	28.6%	0.0032
2 y	27/34	79.4%	3/10	30%	0.0041
3 y	22/25	88%	4/10	40%	0.0044
4 y	13/16	81.3%	3/10	30%	0.0082
5 y	11/13	84.6%	2/5	40%	0.0661

donor age and sex. The 5-year actuarial patient survival was 100% in the FK506 group. The 1-year, 3-year, and 5-year graft survivals were 94.7%, 86.8%, and 86.8% for the FK506 group, and 93.6%, 87.8%, and 82.3% for the CyA group, respectively (Fig. 1). These differences were not statistically significant.

The incidence of acute rejection within the first 90 days was 31.6% in the FK506 group which was lower than the 57.1% of the CyA group, although not significantly so ($P = 0.0585$). In contrast, the incidence of rejection in the FK506 group was significantly lower during the first 30 days after transplantation than in the CyA group (26.3% vs 53.1%; $P = 0.0469$). Steroid-resistant rejection occurred in 21.1% of the FK506 patients and in 32.7% of the CyA patients. All rejection episodes in the FK506 group were confirmed histologically by renal biopsy. Twenty percent of the acute rejection episodes were more severe than grade IIA in the FK506 group and 37% in the CyA group (Tables 1, 2).

The mean ± SD oral dosage of FK506 was 0.172 ± 0.089 mg/kg per day at 1 month after transplantation and was 0.085 ± 0.029 mg/kg per day at 1 year after transplantation. The mean FK506 dosages were 0.061 ± 0.024 and 0.04 ± 0.017 mg/kg per day at 3 and 5 years, respectively (Fig. 2). The mean 12-h whole blood trough levels were 13.5 ± 6.9 ng/ml, 5.0 ± 2.4 ng/ml, 5.1 ± 3.4 ng/ml, and 2.7 ± 1.1 ng/ml at 1 month, and 1, 3, and 5 years, respectively (Fig. 3). The mean FK506 dose and mean FK506 trough level were significantly lower than the dose used in the phase III clinical study of FK506 in Japan. The required steroid dose was lower in the FK506 group than in the CyA group.

The mean serum creatinine concentrations were similar between patients receiving either FK506 or CyA. The serum creatinine concentration was relatively stable throughout the study period and was within the range 1.3–1.5 mg/dl. The incidence of the development of diabetes was 27.8% in the FK506 group and 17.1% in the CyA group. This difference was not statistically significant. The incidence of insulin-dependent diabetes was 10.5% in the FK506 group and 4.3% in the CyA group. Hyperglycemia requiring insulin therapy oc-

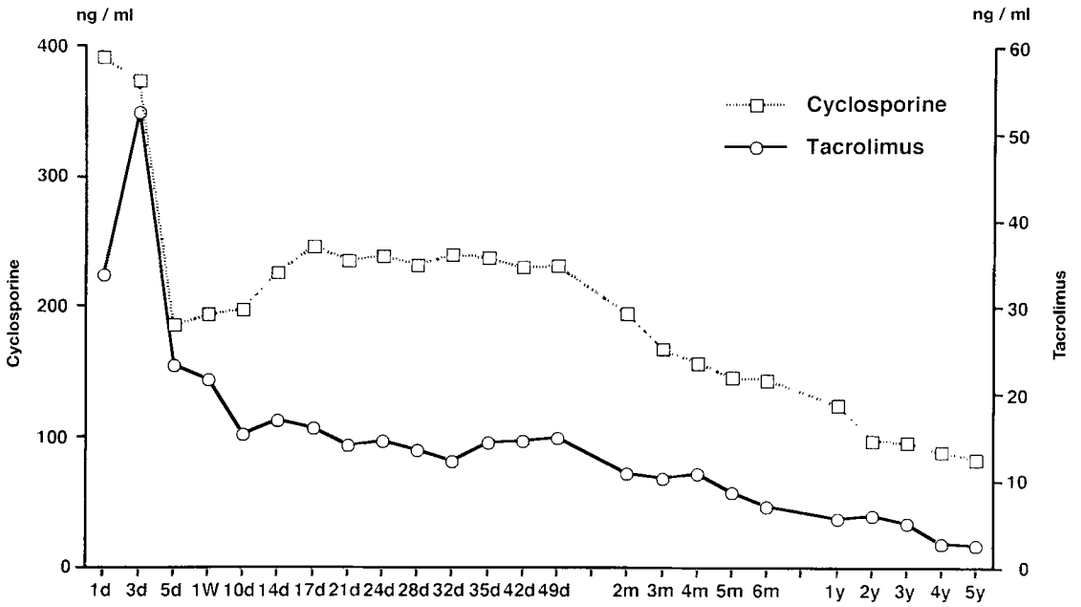

Fig. 3 Whole blood trough level in tacrolimus and cyclosporine

curred more frequently in the FK506 group than in the CyA group. However, insulin therapy was discontinued in all patients of the FK506 group within 5 months. The percentage of patients who required an antihypertensive agent was 28.6, 30, and 40% in the FK506 group and 73.2, 79.4, and 88% in the CyA group at 1, 2, and 3 years, respectively (Table 3). The differences between the two group were statistically significant at each time point.

The incidence of other adverse events are listed in Tables 4 and 5. Nephrotoxicity was confirmed by renal biopsy. Nephrotoxicity was observed in 20% of the patients in the FK506 group and 14.3% of the patients in the CyA group. Hypercholesterolemia occurred less frequently in the FK506 group than in the CyA group. However, the incidence of nephrotoxicity, hyperkalemia, and hypercholesterolemia in the FK506 group were not significantly higher than the CyA group.

Table 5 Adverse effects

	Cyclosporine	Tacrolismus	*P*
Hyperkalemia (> 5.4 mE/l)	13 (26.5%)	19 (26.3%)	
Hypercholesterolemia (> 240 mg/dl)			
At 6 months	50%	15.4%	0.0065
At 1 year	65.6%	16.7%	0.002
At 2 years	60%	41.7%	0.2659
At 3 years	58.8%	50%	0.8402
Hyperuricemia (> 7.5 mg/dl)			
At 6 months	62.5%	50%	0.4151
At 1 year	52.6%	66.7%	0.3888
At 2 years	63.6%	72.7%	0.5769
At 3 years	60.9%	66.7%	0.7352

Discussion

While several animal and human studies have demonstrated the efficacy of FK506 as the primary prophylac-

Table 4 Histological summary of graft biopsies treated with cyclosporine or tacrolismus (57 biopsies from 28 patients treated with cyclosporine, 39 biopsies from 15 patients treated with tacrolismus)

	Cyclosporine		Tacrolismus	
	Patients (n = 28)	Biopsies (n = 57)	Patients (n = 15)	Biopsies (n = 39)
Rejection	15 (53.6%)	34 (59.6%)	3 (20.0%)	14 (35.9%)
Drug-associated arteriolopathy	3 (10.7%)	4 (7.0%)	1 (6.7%)	2 (5.1%)
AR(or CR) + arteriolopathy	3 (10.7%)	5 (8.8%)	3 (20.0%)	3 (7.7%)
AR(or CR) + nephrotoxicity	1 (3.6%)	2 (3.5%)	1 (6.7%)	2 (5.1%)
Nephrotoxicity	3 (10.7%)	3 (5.3%)	2 (13.3%)	1 (2.6%)
NP or other	2 (7.1%)	9 (15.8%)	4 (26.7%)	17 (43.6%)

tic medication for the prevention of acute rejection in solid organ transplantation, toxicities are associated with its use [2–6]. Nephrotoxicity [6, 7, 10, 11], neurotoxicity [8], and altered glucose metabolism [9, 12] are the most clinically important toxic complications. As a result a low-dose FK506-based regimen has been developed to reduce the adverse effects of this drug. In this study, the mean FK506 dose and the mean FK506 trough level were significantly lower than those reported in the phase III clinical study of FK506 in Japan [13–15]. However, results of the present study also showed that FK506 is as effective as CyA in terms of patient and graft survival following renal transplantation. The incidence of acute rejection within the first 30 days in the FK506 group was significantly lower than that of the CyA group. The incidence of acute rejection within the first 90 days in the FK506 group was lower than that of the CyA group and there may be a trend to less rejection.

The toxicities of FK506 are well described and include nephrotoxicity and diabetes. However, the side effects are seen at a similar frequency if CyA is used for immunosuppression. In contrast, patients receiving FK506 require lower dose of antihypertensive medication. In summary, the FK506-based regimen described above reduces the adverse effects associated with the drug. The whole blood FK506 concentration should be monitored and blood levels maintained in the 5–10 ng/ml range 90 days after transplantation for optimal efficacy and minimal toxicity.

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