JACC Vol. 25, No. 5
April 1995:1183–8

Immunosuppression Switch in Pediatric Heart Transplant Recipients: Cyclosporine to FK 506

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Objectives. **We studied rejection, allograft function and side effects, such as hypertension, renal dysfunction and hypercholesterolemia, in seven patients switched from cyclosporine-based triple-drug immunosuppression to FK 506.**

Background. **A subset of pediatric heart transplant recipients treated with triple-drug immunosuppression consisting of cyclosporine, azathioprine and prednisone experience either persistent rejection when attempts are made to taper corticosteroids or morbidity from cyclosporine and corticosteroids. Experience with the new immunosuppressive agent FK 506 has demonstrated its effectiveness as a single agent in heart transplant recipients, and anecdotal evidence has shown that side effects such as hypertension and hypercholesterolemia may be lower.**

Methods. **Seven patients whom we deemed corticosteroid dependent were switched to FK 506–based therapy. Allograft function, episodes of rejection, need for corticosteroids and incidence of side effects from FK 506 were monitored. The switch to FK 506 was performed using an established protocol. Follow-up time has ranged from 15 to 41 months. Serial right heart catheterizations and endomyocardial biopsies were performed after each reduction of corticosteroid dosing.**

Results. **Catheterization data showed no significant change in pulmonary wedge pressure, mean right atrial pressure or cardiac index, indicating no decline in allograft function. Serial echocardiographic variables of allograft function were also stable. At present, all seven patients are free of the corticosteroid portion of their immune suppression. There have been only two episodes of significant acute rejection requiring treatment with intravenous corticosteroids. Antihypertensive medications have been discontinued in five of six patients previously treated with these drugs. Plasma cholesterol, low density lipoprotein and triglyceride levels were decreased, and renal function was stable.**

Conclusions. **Preliminary studies suggest that FK 506 may be an alternative immunosuppressive agent for pediatric and adolescent patients experiencing ongoing rejection or significant morbidity from cyclosporine and corticosteroids and in those patients dependent on corticosteroids for immune suppression.**

(J Am Coll Cardiol 1995;25:1183–8)

Triple-drug immunosuppression regimens including cyclosporine, azathioprine and prednisone have greatly improved survival after cardiac transplantation in children. Despite the success of this regimen, there are patients who experience persistent focal graft rejection (International Society of Heart and Lung Transplantation [ISHLT] grades 2, 3A and 3B) when corticosteroids are tapered or discontinued. In addition, some patients experience adverse effects related to the cyclosporine and prednisone combinations, such as hypertension, hyperlipidemia, migraine headaches, obesity, Cushingoid appearance and behavioral changes (1–5). Studies in adult and pediatric patients have suggested that side effects, such as hypertension, obesity and hypercholesterolemia, may jeopardize long-term allograft function and increase the likelihood for the development of obliterative coronary artery disease (6–8).

Since 1989, FK 506–based immune suppression has been used for pediatric heart transplant recipients in Pittsburgh (9,10). This newer immunosuppressive agent has a mechanism similar to that of cyclosporine, involving suppression of cytokine gene transcription and prevention of T-cell activation (11). Early in that experience, we found that FK 506 alone was as effective as the triple-drug regimen for maintenance therapy in most patients. Our management philosophy has always been to eliminate corticosteroids from the immune suppression regimen as soon after transplantation as feasible. The purpose of the present study was to determine the effectiveness of FK 506 with or without azathioprine for preventing rejection while maintaining overall graft function. A subset of pediatric and adolescent heart transplant recipients who had persistent rejection or morbidity related to the cyclosporine and prednisone combination was selected for this investigation.

Methods

Study patients. The study included seven pediatric and young adult patients, 8.9 to 20.5 years old at the time study, who had previously undergone orthotopic heart transplantation between ages 1.1 and 16.3 years. Transplantation was performed at the University of Pittsburgh between January 1987 and July 1989. All patients originally had induction therapy with antithymocyte globulin (rabbit) and maintenance

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Manuscript received December 3, 1993; revised manuscript received October 7, 1994, accepted December 8, 1994.

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0735-1097/95/$9.50
0735-1097(94)00551-Z

Table 1. Demographic Information and Reason for the Switch to FK 506 in the Study Patients

Pt No./Age at Tx (yr)	Reason for Immunosuppression Switch	CyA Levels Before Switch (ng/ml)	Time From Tx to Switch (mo)
1/11.6	Chronic rejection	FPIA 1,091, HPLC 233	9
2/11.11	Chronic rejection	FPIA 696, HPLC 193	15
3/16.3	Corticosteroid morbidity: hyperlipidemia	FPIA 812, HPLC 223	26
4/2.2	Chronic rejection; corticosteroid morbidity: hypertension, delayed growth, migraines, behavioral problems	FPIA 325, HPLC 125	57
5/12.9	Chronic rejection	FPIA 915, HPLC 235	45
6/7.11	Corticosteroid morbidity: hypertension, behavioral problems	FPIA 292, HPLC 91	58
7/1.10	Corticosteroid morbidity: hyperlipidemia, delayed growth	FPIA 1,235, HPLC 371	34

CyA = cyclosporine A; FPIA = whole blood fluorescence polarization immunoassay; HPLC = high pressure liquid chromatography; Pt = patient; Tx = transplantation.

triple-drug immune suppression with cyclosporine, corticosteroids and azathioprine (9,12). Study patients were chosen to undergo the switch to FK 506 because of persistent cellular rejection on endomyocardial biopsy when prednisone was tapered (4) or significant morbidity related to cyclosporine and prednisone, or both (4). The time between transplantation and the switch to FK 506 immunosuppression ranged from 9 to 58 months (mean [±SD] 35 ± 19). Table 1 details patient demographic information and the reason for the immunosuppression switch in each patient.

The first five patients were hospitalized for the switch to FK 506 so that blood pressure, urine output, serum blood urea nitrogen, serum creatinine, serum electrolytes, serum glucose and plasma drug levels could be monitored closely. The remaining two patients underwent the switch to FK 506 on a closely supervised outpatient basis in the Pittsburgh area. The designated drug protocol is outlined in Table 2. Informed consent was obtained from all patients and their families before the change in immunosuppressive agents.

Episodes of rejection were monitored by endomyocardial biopsy 2 weeks after the switch to FK 506 and after each reduction of the corticosteroid dosage. Major rejection episodes were defined as histologic evidence of significant interstitial lymphocyte infiltration or myocyte necrosis, ISHLT classification grades 2 to 3B. Pathologists grading the degree of rejection on surveillance biopsy specimens obtained after the switch had no knowledge of the type of immunosuppression used.

Table 2. Summary of Drug Protocol Used to Switch From Cyclosporine to FK 506

1. Discontinue CyA 72 h before starting FK 506
2. Initiate FK 506: 0.2 mg/kg per day BID dosing
3. Maintain all other immune suppression
4. Monitor renal function, potassium and glucose
5. Target FK 506 level: 0.5 to 1.5 ng/ml

BID = twice a day; CyA = cyclosporine A.

Allograft function determination was followed by right heart catheterization, echocardiography and electrocardiography at the time of endomyocardial biopsy. Patients underwent monthly laboratory evaluation, including FK 506 plasma level, complete blood count and differential, renal function tests, serum electrolytes, serum glucose and liver function tests, including alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase and total/direct bilirubin. Complete lipid panels, including total cholesterol, low density lipoprotein (LDL), high density lipoprotein and triglyceride levels, were performed in all patients at 3- to 6-month intervals.

After the switch from cyclosporine to FK 506–based immunotherapy all patients were continued on maintenance prednisone at a dose of 0.1 to 0.3 mg/kg body weight per day. This subset of pediatric heart transplant recipients included six of seven patients who could not be weaned from corticosteroids because of evidence of ongoing rejection. The prednisone dose was decreased by 50% increments every 3 months after a negative biopsy result (ISHLT grades 1A and 1B only). Prednisone was discontinued from a dosage of 2.5 mg or 0.1 mg/kg.

All seven patients included in this study were treated initially with cyclosporine, azathioprine and corticosteroids for 9 to 58 months (mean [±SD] 35 ± 19) after heart transplantation, and they were continued on their maintenance dose of azathioprine after the switch to FK 506. Prednisone was weaned and discontinued first. If patients continued to have no signs of rejection on endomyocardial biopsy, azathioprine was then stopped. Currently, azathioprine has been discontinued in five of seven patients, and will soon be stopped in the remaining two.

Statistics. The Student *t* test for paired observations was used to compare differences between triple-drug suppression

Table 3. Summary of Right Heart Hemodynamic and Echocardiographic Data From Pediatric Patients 9 to 12 Months Before and After the Switch to FK 506 Immunosuppression

	CyA		FK 506		
	Range	Mean ± SD	Range	Mean ± SD	p Value
Echocardiographic Data					
Left ventricular shortening fraction	0.30–0.49	0.36 ± 0.03	0.30–0.41	0.36 ± 0.03	0.77
Interventricular septal thickness (mm)	6–12	8.7 ± 1.4	6–10	9 ± 0.9	0.42
Left ventricular posterior wall thickness (mm)	6–10	8.4 ± 1.4	6–11	8.7 ± 1.3	0.65
Left ventricular end-diastolic dimension (mm)	30–54	41 ± 6	30–54	41 ± 7	0.96
Catheterization Data					
Pulmonary artery wedge pressure (mm Hg)	5–16	8.8 ± 1.6	5–15	9.1 ± 2.7	0.21
Mean right atrial pressure (mm Hg)	1–7	4.1 ± 0.9	1–8	4.5 ± 1.7	0.13
Cardiac index (liters/min per m^2)	2.3–5.3	3.8 ± 1.1	2.5–5.1	3.9 ± 0.8	0.45

CyA = cyclosporine A.

and FK 506 mean values. Each patient served as his or her own control after the switch in immunosuppressive agents; however, because of the small sample size, statistical analysis should be viewed with caution. Results are reported as mean value ± SD, and $p < 0.05$ was considered significant.

Results

Allograft function. All seven patients maintained stable allograft function after being switched to FK 506. Table 3 shows right heart hemodynamic and echocardiographic data 9 to 12 months before and after the switch to FK 506. There has been no graft loss or documented coronary artery disease in our study patients.

Allograft rejection. Endomyocardial biopsy results for all seven patients are presented in Figure 1. In the first 6 months after the change to FK 506, there were six episodes of rejection (ISHLT grades 2 to 3A) in seven patients. Five episodes resolved with a dose increase in FK 506, and only one required treatment with intravenous corticosteroids. In fact, as noted in Figure 1, there have been only two episodes of acute rejection that required treatment with intravenous corticosteroids since the switch to FK 506–based immune suppression. One was in the initial period after the switch to FK 506 in a patient with chronic rejection, and the second was associated with a patient's noncompliance with FK 506. During the entire follow-up time (mean follow-up 24 months, range 15 to 41), there have been no episodes of significant acute rejection when the FK 506 level was within the therapeutic range of 0.5 to 1.5 ng/ml. All seven patients have been weaned from prednisone and are free of the corticosteroid portion of their immune suppression. With the discontinuation of long-term oral prednisone, the four patients who were switched to FK 506 because of corticosteroid morbidity had a resolution of Cushingoid features, migraine headaches, growth delay and behavioral problems.

Complications of immune suppression. *Hypertension.* Six (85%) of seven of the patients required one or more antihypertensive medications to control blood pressure while receiving triple-drug immunosuppression. Since switching to FK 506 antihypertension medication has been discontinued in all seven patients (Table 4). In one patient, hypertension resurfaced in association with declining renal function 2 years after switching to FK 506 immune suppression and 6 years after transplantation.

Hyperlipidemia. When immunotherapy included cyclosporine and corticosteroids, 71% of our study group had serum cholesterol and triglyceride levels >95th percentile for age (12). Since the switch to FK 506, all patients have had a decrease in the mean values of total serum cholesterol, triglycerides and LDL levels (Table 4). Total cholesterol values during triple-drug immunosuppression ranged from 161 to 263 mg/dl (mean 217 [SD 35.6]) and decreased to 95 to 193 mg/dl (mean 149 [SD 34.1]) during FK 506 therapy. Triglyceride levels before the switch were 83 to 271 mg/dl (mean 193 [SD 73.2]) and decreased to 80 to 216 mg/dl (mean 127 [SD 47]) after the switch. Low density lipoprotein cholesterol ranged from 85 to 193 mg/dl (mean 143 [SD 35.6]) before the switch and from 41 to 141 mg/dl (mean 97 [SD 33.6]) after the change to FK 506 therapy.

Renal function. Renal function has been monitored closely. One year after the switch to single-drug immunosuppression with FK 506 there has been no statistically significant increase in blood urea nitrogen or creatinine values (Table 4). Mean blood urea nitrogen values on triple-drug immunosuppression 1 year before the switch were 14 to 43 mg/dl (mean 28 [SD 9]) and increased to 22 to 37 mg/dl (mean 30 [SD 6]) after the switch to FK 506. Mean creatinine ranged from 0.5 to 1.4 mg/dl (mean 1.1 [SD 0.37]) before the switch to FK 506 and increased to 0.8 to 1.6 mg/dl (mean 1.26 [SD 0.26]) 1 year after the change in immunosuppression. Neither the increase in mean blood urea nitrogen nor the increase in mean creatinine was statistically significant ($p = 0.59$ and $p = 0.37$, respectively).

Malignancy. As shown in Figure 1, Patient 1 developed symptomatic posttransplant lymphoproliferative disease ~1 year after being switched to FK 506. This lymphoid tumor is

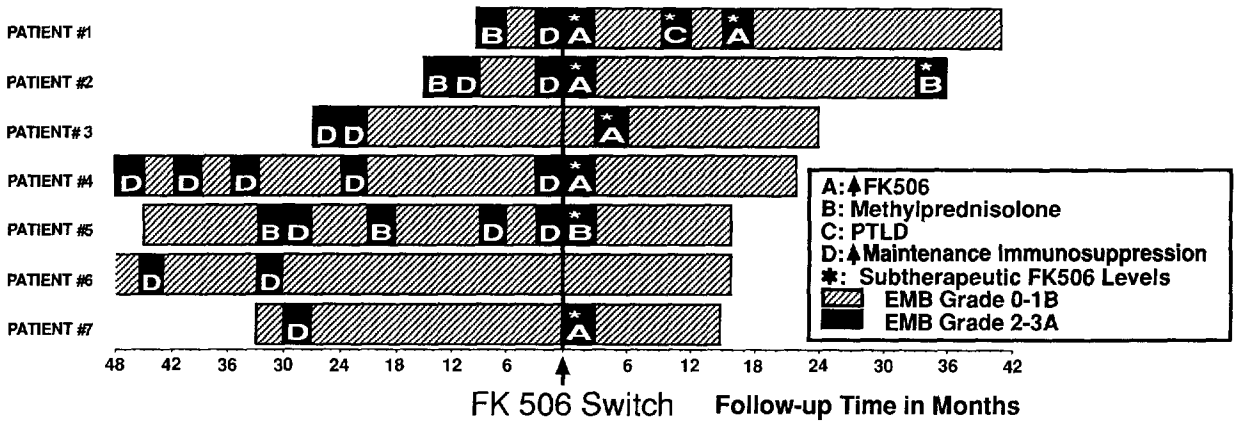

Figure 1. Endomyocardial biopsy (EMB) results before and after immune suppression was changed to FK 506. PTLD = posttransplant lymphoproliferative disease.

associated with Epstein-Barr viral infection in immunocompromised hosts. Typically, the tumor regresses with reduction of immunosuppression alone, as it did in this patient.

Discussion

In October 1989 a prospective clinical trial was begun using FK 506 and low-dose steroids as the sole immunosuppression regimen in patients undergoing orthotopic cardiac transplantation (10). Results of that study were encouraging, particularly in the pediatric patients who previously were particularly troublesome compared with their adult counterparts in controlling allograft rejection. Also noted in that trial was a new degree of flexibility in immunosuppressant management with the ability to reverse episodes of grade 2 to 3A rejection by merely increasing the oral dosage of FK 506. In addition, 80% of the study patients were successfully weaned from corticosteroids and tolerated FK 506 with minimal adverse effects.

Approximately 10% to 15% of our pediatric heart transplant recipients who had undergone transplantation before October 1989 and were treated with traditional triple-drug immunosuppression experienced persistent allograft rejection when attempts were made to taper or discontinue corticosteroids. Several of these patients were also experiencing morbidity secondary to cyclosporine and corticosteroids, such as hypertension, hyperlipidemia, obesity, migraine headaches and behavioral problems. It was in this context that we decided to switch these patients from cyclosporine to FK 506–based immune suppression.

Allograft rejection. Nine episodes of rejection (ISHLT grade 2 to 3B) occurred in six allografts after the switch from cyclosporine to FK 506 during the follow-up period of 170 months. These episodes all occurred when FK 506 levels were subtherapeutic, and most were treated with augmented dosing of FK 506 alone. Only two episodes were considered severe enough to require intravenous methylprednisolone. Currently, all patients are free of the corticosteroid portion of their

Table 4. Antihypertensive Medications, Renal Function and Serum Lipid Values in the Study Patients Before and After the Switch in Immunosuppression

	Before Switch						After Switch					
		Renal Function		Serum Lipid Levels				Renal Function		Serum Lipid Levels		
Pt No.	Antihypertensive Medication	BUN	Cr	T. Chol	TG	LDL	Antihypertensive Medication	BUN	Cr	T. Chol	TG	LDL
1	Captopril	29	1.1	161	270	85	None	29	1.4	95	107	41
2	Diltiazem	14	0.5	196	83	126	None	36	1.3	145	80	93
3	Captopril	29	1.4	263	233	193	None	22	1.1	193	216	141
4	Nifedipine	43	1.4	260	271	173	Nifedipine	37	1.4	178	163	129
5	Captopril; cardiozem	24	1.2	216	129	141	None	30	1.2	125	97	75
6	Captopril	33	1.4	210	217	124	None	34	1.6	172	117	109
7	None	23	0.7	213	151	157	None	23	0.8	136	106	92
Median		29	1.2	213	217	141		30	1.3	145	107	93
Mean		28	1.10	217	193	143		30	1.26	149	127	97
p value								0.59	0.37	0.003	0.06	0.03

BUN = blood urea nitrogen; Cr = creatinine; LDL = low density lipoprotein; Pt = patient; T. Chol = total cholesterol; TG = triglyceride.

immunosuppressive regimen. The need for corticosteroids as part of maintenance immune suppression in children has been questioned in at least three reported studies (13–15). Despite these observations, our experience has identified a group of cardiac allograft recipients who have required corticosteroids as part of their immune suppression regimen. The present study has identified the effectiveness of FK 506 immune suppression in this small subset of patients.

Allograft function. We used serial right heart catheterization and echocardiography to document stable allograft function during and after the switch in immune suppression regimen. Comparison of hemodynamic data, cardiac index and echocardiographic variables of allograft function before and up to 3 years after the switch to FK 506 indicated no decline in overall graft function.

Hypertension and hyperlipidemia. Previous studies have documented a 40% to 70% incidence of hypertension in transplant recipients receiving cyclosporine with or without corticosteroids (1,10). Not only does the increased afterload from hypertension adversely affect the transplanted heart, but drugs used for treatment, such as angiotensin-converting enzyme inhibitors, also may threaten already compromised renal function (16). All seven of our patients were able initially to discontinue one or more antihypertensive medications after the switch to FK 506 as a single immunosuppressive agent. The switch to FK 506 allowed resolution of corticosteroid-induced hypertension and hypercholesterolemia. Uzark et al. (2) studied hypercholesterolemia after cardiac transplantation in children receiving prednisone, cyclosporine and azathioprine and found that within 2 to 12 months (mean 8.5) after cardiac transplantation, 12 (86%) of 14 had a total serum cholesterol level above the 90th percentile for age by Bogalusa criteria (13) and >190 mg/dl. They concluded that hyperlipidemia, specifically hypercholesterolemia, is a common problem in children >2 years of age after cardiac transplantation. Mean serum cholesterol and triglyceride values were above the 95th percentile for age in 71% of our study patients when immunosuppression included cyclosporine and prednisone; after the switch to FK 506, each patient had a decrease in total cholesterol, triglyceride and HDL levels. Gao et al. (6) studied the clinical and laboratory correlates of accelerated coronary artery disease in adult cardiac transplant patients and also noted that elevated plasma triglyceride levels were a significant predisposing factor for the development of posttransplant coronary artery disease.

Renal function. The clinical trial of FK 506 in pediatric cardiac transplant patients at the University of Pittsburgh found that renal dysfunction in these patients had been modest (12). Each of our seven patients had a mild increase in blood urea nitrogen and creatinine values 1 year after the switch to FK 506, but, this increase was not statistically significant. Experience with both FK 506 and cyclosporine has shown similar nephrotoxicity profiles (16,17). Within 1 year after transplantation serum creatinine levels double, which is out of proportion to somatic growth regardless of immune suppression. One year after the switch to FK 506–based immune suppression there was no statistically significant change in blood urea nitrogen or creatinine values in any of our seven study patients. Currently two patients have moderate to severe renal dysfunction, which was present after several years of cyclosporine-based immune suppression regimens. Renal dysfunction continued to progress after the switch to FK 506. Both of these patients will require renal transplantation in the future. We are concerned about long-term renal function in patients taking both cyclosporine and FK 506. Differences in long-term renal function in patients managed on cyclosporine versus FK 506 are not known.

Summary and conclusions. FK 506 is an alternative immunosuppressive agent for patients experiencing ongoing rejection or significant morbidity from cyclosporine and corticosteroids. Although our study is limited by its small size, all patients were able to switch successfully to FK 506 with no increase in the incidence of rejection or decline in allograft function. We speculate that the reason that patients were able to do well with FK 506 alone may be related to its substantial immunosuppressive effect, shown in vitro to be greater than that of cyclosporine A (18). Hypertension and hyperlipidemia improved when cyclosporine and corticosteroids could be eliminated from the immune suppression regimen. Other side effects secondary to corticosteroids, such as obesity, migraine headaches and behavioral problems resolved after discontinuation of long-term oral prednisone. The adverse effects of FK 506 in our study patients were mild and manageable. This preliminary study suggests that immunosuppression with FK 506 may be a feasible alternative in a similar subset of pediatric patients. Further studies, including a larger randomized double-blind investigation of patients throughout the pediatric age range, will be important for future management.

References

1. Addonizio L, Hsu D, Smith C, Gersony W, Rose E. Late complications in pediatric cardiac transplant recipients. Circulation 1990;82 Suppl IV:IV-295–301.
2. Uzark K, Crowley D, Callow L, Bove E. Hypercholesterolemia after cardiac transplantation in children. Am J Cardiol 1990;66:1385–7.
3. Becker D, Chamberlain B, Swank R, et al. Relationship between corticosteroid exposure and plasma lipid levels in heart transplant recipients. Am J Med 1988;85:632–8.
4. Ballantyne C, Podet E, Patsch W, et al. Effects of cyclosporine therapy on plasma lipoprotein levels. JAMA 1989;262:53–6.
5. Ballantyne C, Jones P, Payton-Ross C, et al. Hyperlipidemia following heart transplantation: natural history and intervention with mevinolin (lovastatin). Transplant Proc 1987;19 Suppl 5:60–2.
6. Gao S, Shroeder J, Alderman E, et al. Clinical and laboratory correlates of accelerated coronary artery disease in the cardiac transplant patient. Circulation 1987;76 Suppl V:56–61.
7. Pahl E, Fricker F, Armitage J, et al. Coronary arteriosclerosis in pediatric heart transplant survivors: limitation of long-term survival. J Pediatr 1990; 116:177–83.
8. Uretsky B, Murali S, Reddy P, et al. Development of coronary artery disease in cardiac transplant patient receiving immunosuppressive therapy with cyclosporine and prednisone. Circulation 1987;76:827–33.
9. Armitage J, Fricker F, delNido P, et al. A decade (1982–1992) of pediatric cardiac transplantation and the impact of FK 506 immunosuppression. J Thorac Cardiovasc Surg 1993;105:464–73.
10. Armitage J, Fricker J, del Nido P, Cipriani L, Starzl T. The clinical trial of FK 506 as primary and rescue immunosuppression in pediatric cardiac transplantation. Transplant Proc 1991;23:3058–60.

11. Morris R. Immunopharmacology of new xenobiotic immunosuppressive molecules. Semin Nephrol 1992;12:304–14.
12. Addonizio L, Rose E. Cardiac Transplantation in children and adolescents. J Pediatr 1987;6:1034–8.
13. Berenson GS, ed. Causation of Cardiovascular Risk Factors in Children—Perspective on Cardiovascular Risk in Early Life. New York: Raven Press, 1986:40–346.
14. Renlud D, O'Connell J, Gilbert E, Watson F, Bristow M. Feasibility of discontinuation of corticosteroid maintenance therapy in heart transplantation. J Heart Transplant 1987;6:71–8.
15. Au J, Gregory J, Colquhoun I, et al. Paediatric cardiac transplantation with steroid-sparing maintenance immunosuppression. Arch Dis Child 1992;67: 1262–6.
16. Fung J, Alessiani M, Abu-Elmagd K, et al. Adverse effects associated with the use of FK 506. Transplant Proc 1991;23:3105–8.
17. McCauley J, Fung J, Jain A, Todo S, Starzl T. The effects of FK 506 on renal function after liver transplantation. Transplant Proc 1990;22:17–21.
18. Zeevi A, Duquesnoy RJ, Eiras G, Todo S, Makowka L, Starzl TE. In vitro immunosuppressive effects of FK-900506 on human T cells alloactivation. Surg Res Commun 1987;1:315.