

1999

Clinical features of acute reversible tacrolimus (FK 506) nephrotoxicity in kidney transplant recipients

SR Katari, M Magnone, R Shapiro, M Jordan, V Scantlebury, C Vivas, A Gritsch, J McCauley, T Starzl, AJ Demetris, PS Randhawa. Clinical features of acute reversible tacrolimus (FK 506) nephrotoxicity in kidney transplant recipients. Clin Transplantation 1997; 11: 237-242. © Munksgaard, 1997

This study was designed to (a) estimate the contribution of tacrolimus nephrotoxicity to episodes of renal allograft dysfunction investigated by needle biopsy, (b) describe the temporal evolution of nephrotoxicity and its response to therapy, and (c) ascertain how often renal dysfunction is associated with concurrent extra-renal toxicity.

Patients were selected based on a rising serum creatinine, normal ultrasound, and biopsy findings leading to a reduction in the dose of tacrolimus and a fall in serum creatinine. Twenty two (17%) cases of nephrotoxicity were identified amongst 128 consecutive kidney transplant biopsies with sufficient clinical data for analysis.

There were 13 males and 9 females, 17-75 yr in age. Tacrolimus was administered initially as a 0.075-0.1 mg/kg/d IV continuous infusion followed by an oral dose of 0.15 mg/kg twice daily. The onset of nephrotoxicity in this study occurred 1-156 wk post-operatively. The mean baseline creatinine was 212.2 ± 168.0 $\mu\text{mol/l}$ (range 88.4-875.2) and rose $40.6\% \pm 14.2\%$ (range 11-66) during episodes of nephrotoxicity ($p < 0.001$). The highest recorded plasma and whole-blood tacrolimus levels during the toxic episodes were respectively 2.7 ± 0.8 ng/ml (range 1.1-3.5) and 31.6 ± 10.6 ng/ml (range 14.5-50.5). The drug levels were considered to be beyond the therapeutic range in 18/22 (82%) patients. The highest tacrolimus level preceded the rise in serum creatinine in 20 cases by an interval of 1.6 ± 1.8 d. A mean reduction in tacrolimus dosage of $41\% \pm 21\%$ (range 11-89) led to a $86\% \pm 18\%$ (range 45-100) fall in the serum creatinine within 1-14 d ($p < 0.001$). Interactions between tacrolimus and clarithromycin, diltiazem, or itraconazole modified the pharmacokinetic parameters in three cases. Serum potassium > 5.0 mequiv/l was recorded in 9/22 (41%) cases. Three or more elevations in blood glucose > 7.7 mmol/l (140 mg/dl) were recorded in 4/11 (36%) non-diabetic patients. Hand tremors were seen in two (9%) cases and elevated diastolic blood pressure > 90 mmHg in seven (32%) patients.

In conclusion, tacrolimus nephrotoxicity accounted for 17% of graft dysfunction episodes investigated by biopsy. Concurrent hyperglycemia, hyperkalemia, or tremors were noted in several patients. Nephrotoxicity responded well to reduction in the drug dosage.

S. R. Katari, M. Magnone, R. Shapiro, M. Jordan, V. Scantlebury, C. Vivas, A. Gritsch, J. McCauley, T. Starzl, A. J. Demetris and P. S. Randhawa

Divisions of Transplantation, Pathology, Transplantation Surgery, Transplantation Medicine and Urology, Departments of Pathology, Surgery and Medicine, and The Thomas E. Starzl Transplantation Institute, University of Pittsburgh, PA, USA

Key words: tacrolimus - FK 506 - nephrotoxicity - kidney - transplantation

Parmjeet S. Randhawa M. D. Division of Transplantation Pathology, C903.1, Presbyterian University Hospital, Pittsburgh, PA 15213, USA

Accepted for publication 5 September 1996

Tacrolimus (Fujisawa, USA Inc.) is an effective primary immunosuppressive agent following kidney transplantation (1-7). It has both short-term and long-term advantages over conventional drugs (5).

Thus, tacrolimus is associated with less hypertension and hypercholesterolemia than is cyclosporine (1). Nephrotoxicity is well recognized, but with the exception of the Japanese Multicenter trial (6),

which describes its occurrence in up to 44% of patients, its incidence has not been specifically determined in most studies on renal transplant recipients. The estimated incidence of tacrolimus nephrotoxicity in liver transplant recipients varies from 18 to 42% (8–11). These latter figures may not be directly applicable to the kidney transplant population, since liver disease impairs tacrolimus metabolism, thereby increasing the potential for toxicity. Furthermore, the diagnosis of tacrolimus nephrotoxicity in liver transplant patients is confounded by renal dysfunction due to sepsis, hepato-renal syndrome, hepatic glomerulopathy and the use of other nephrotoxic drugs. Heart and lung transplant recipients are not subject to some of these variables, but published studies on these patients again do not attempt to define precisely the magnitude of tacrolimus nephrotoxicity in this clinical setting (12, 13). A detailed clinical description of patients undergoing tacrolimus-induced renal dysfunction is also lacking in much of the available literature. Many studies provide comparative data on groups of patients receiving either tacrolimus or cyclosporine without analyzing each episode of toxicity separately (8, 9, 11, 14–16). The purpose of the present study is therefore to estimate the incidence of tacrolimus nephrotoxicity in episodes of renal allograft biopsy investigated by needle biopsy, to describe its temporal evolution and response to therapy in individual patients, and to ascertain how often it is associated with concurrent extra-renal toxicity.

Methods

Patients were selected over a four year period from July 1991 to July 1995 from a database maintained by the Thomas E. Starzl Transplantation Institute, based on the following criteria: 1. Use of tacrolimus as the primary immunosuppressant after kidney transplantation. 2. Availability of a biopsy performed for rising serum creatinine. Serum creatinine was performed daily in the immediate post-transplant period, biweekly or weekly in the first 8–12 wk after transplantation, and gradually reduced to monthly estimations thereafter. 3. Absence of acute rejection at biopsy leading to reduction in the dose of tacrolimus. 4. Fall of serum creatinine within a 2-wk period following biopsy and reduction in immunosuppression. 5. Clinical exclusion of other causes of graft dysfunction such as vascular and technical problems.

Twenty-two (17%) cases of tacrolimus nephrotoxicity were identified from 128 consecutive biopsies with adequate clinical data available for analysis. The medical records of these patients were analyzed in detail with particular attention to serial changes in serum creatinine, serum potassium,

blood glucose, and alterations in the drug dosage. For outpatients, the last available serum creatinine was recorded as the baseline. In hospitalized patients the lowest value within the 14 d preceding the allograft biopsy was regarded as the basal serum creatinine. The highest serum creatinine corresponding to the episode of nephrotoxicity was then recorded, to permit calculation of the percentage rise in creatinine. The post-treatment trough creatinine was defined as the lowest measurement recorded within a 14-d period following reduction of immunosuppression. To quantitate the therapeutic response, the fall in creatinine was expressed as a percentage of the pre-treatment rise above baseline. The statistical significance of the initial rise and subsequent fall in serum creatinine was evaluated by the Mann–Whitney test. Trough levels of tacrolimus were monitored either in plasma (n=10) or in whole-blood (n=12) using published methodology (17, 18). The normal therapeutic range of tacrolimus at our institution is considered to be 0.5–1.5 ng/ml in plasma and 5–20 ng/ml in whole blood.

Results

The clinical profile of the patients studied is presented in Table 1. There were 13 males, 9 females, with an age range of 17–75 yr. The indications for kidney transplantation were diabetes (n=11), polycystic disease (n=3), glomerulonephritis, (n=4), IgA nephropathy (n=2), hypertension (n=1) and nephrolithiasis (n=1). After a single preoperative dose of 0.15 mg/kg, tacrolimus was administered postoperatively as a 0.075–0.1 mg/kg/d intravenous continuous infusion followed by an oral maintenance dose of 0.15 mg/kg twice daily after commencement of oral feeding. The onset of tacrolimus nephrotoxicity in this study occurred 1–156 wk postoperatively. The baseline creatinine was 212.2 ± 168.0 $\mu\text{mol/l}$ (range 88.4–875.2) and showed a mean rise of $40.6\% \pm 14.2\%$ (range 11–66) during episodes of nephrotoxicity ($p < 0.001$). The highest mean plasma and whole-blood tacrolimus levels during the toxic episodes were 2.7 ± 0.8 ng/ml (range 1.1–3.5) and 31.6 ± 10.6 ng/ml (range 14.5–50.5), respectively. The drug levels were considered to be beyond the therapeutic range in 18/22 (82%) patients. The highest tacrolimus level preceded the highest serum creatinine in 16 cases by an interval of 1.6 ± 1.8 d. In the remaining two cases the serum creatinine peaked 1 and 2 d respectively prior to the highest tacrolimus level. The dose of tacrolimus was reduced stepwise until a satisfactory response in serum creatinine was obtained. The mean reduction was $41\% \pm 21\%$ (range 11–89), and this was statistically significant ($p < 0.001$). No dose reduction was necessary in case 3, since the elevated tacrolimus level fell spontane-

Table 1. Clinical profile of tacrolimus nephrotoxicity in kidney transplant recipients

#	Sex	Age	Time post-tr (wk)	Baseline creatinine ($\mu\text{mol/l}$)	Peak creatinine ($\mu\text{mol/l}$)	Plasma tacrolimus (ng/ml)	Whole blood tacrolimus (ng/ml)	Tacrolimus (mg/day)	Dose reduction (%)	Final creatinine (% response)*	Potassium peak (mequiv/l)	Glucose peak (mmol/l)	Blood pressure (mmHg)
1	M	53	5	168.0	221.0	2.7		45	15	176.8 (71)	4.7	11.1	188/98
2	M	52	10	168.0	309.4		35.8	10	40	212.2 (69)	NA	IDDM	NA
3	M	44	32	221.0	459.7		14.5	8	0	159.1(100)	4.5	IDDM	110/110
4	F	44	6	150.3	265.2		36.0	28	43	176.8 (77)	5.0	IDDM	140/60
5	F	17	16	150.3	309.4		50.5	8	66	159.1(100)	5.1	6.6	NA
6	F	59	4	176.8	221.0	1.4		28	29	176.8(100)	4.3	13.4	168/90
7	M	40	4	132.6	203.3		17.4	30	27	159.1 (63)	4.9	IDDM	150/84
8	M	43	32	106.1	203.3	1.7		18	89	159.1 (45)	5.0	6.7	136/94
9	F	47	36	238.7	336.0	3.4		10	40	159.1(100)	5.5	IDDM	NA
10	M	58	114	230.1	397.8	2.4		6	66	159.1(100)	5.3	IDDM	190/102
11	F	64	2	150.3	344.8		34.7	18	71	132.6(100)	4.8	9.0	180/90
12	F	68	2	106.1	300.6		26.9	28	29	150.3 (77)	5.3	10.3	130/80
13	F	60	4	159.1	229.8		30.6	28	36	132.6(100)	4.2	28.8	150/80
14	M	35	1	123.8	194.5		40.5	32	38	141.4 (75)	5.7	IDDM	158/92
15	M	52	40	88.4	265.2		19.0	11	11	123.8 (80)	5.0	IDDM	162/102
16	M	65	10	194.5	291.7	3.3		4	50	212.2 (82)	3.7	9.6	NA
17	F	36	156	150.3	247.5	2.7		28	14	194.5 (54)	4.1	IDDM	74/42
18	M	58	12	150.3	282.9	2.5		10	40	150.3(100)	5.6	IDDM	NA
19	M	34	32	274.0	309.4	3.5		22	36	247.5(100)	NA	NA	NA
20	F	75	1	875.2 ^b	1149.2	3.3		20	20	583.4(100)	5.1	17.0	150/80
21	M	49	16	159.1	353.6		34.2	22	36	141.4(100)	5.3	12.7	160/98
22	M	51	1	495.0 ^b	839.8		39.6	20	75	274.0(100)	5.6	6.9	NA

Abbreviations: IDDM, insulin-dependent diabetes melitus; NA, not available; post-tr, post-transplant.

* % response refers to the fall in creatinine expressed as a percentage of the difference between the baseline creatinine and the peak creatinine. Thus, the % response for case 1 is $(221-176.8)/(221-168) \times 100$. Results between 0 and 100% indicate a partial therapeutic response. Cases with a final creatinine equal to or lower than the baseline creatinine are all recorded as 100% response.

^b The high baseline creatinine in these patients studied 1 wk after transplantation reflects the presence of acute tubular necrosis.

ously. In two cases a single dose of solumedrol was empirically administered for possible rejection prior to results of the biopsy becoming available. Reduction in the dose of tacrolimus led to a $86\% \pm 18\%$ (range 45–100) fall in the serum creatinine. The therapeutic response generally commenced within 1–8 d, except in case 8, where a drug interaction with itraconazole delayed the response to 14 d. One or more episodes of hyperkalemia (serum potassium greater than 5.0 mequiv/L) were recorded in 9/22 (41%) cases within 10 d of the peak in serum creatinine. The actual potassium levels fluctuated somewhat, and persistent high values were not always observed. Three or more values of elevated blood glucose exceeding 7.7 mmol/l (140 mg/dl) were recorded in 4/11 (36%) non-diabetic patients. Concurrent use of intravenous steroids adequately explained the hyperglycemia in one patient; in the remainder it was considered to be a transient manifestation of FK 506 toxicity to the pancreas. Hand tremors attributed to tacrolimus neurotoxicity were seen in two (9%) cases (patients 5 and 21). The blood pressure readings in these patients were reviewed to test the notion that tacrolimus exerts its deleterious actions on the kidney by causing vasoconstriction in the renal vascular bed. Elevation in diastolic blood pressure greater than 90 mmHg diastolic was noted in seven (32%) patients. However, day-to-day readings were quite variable, and no pro-

gressive rise coincided with the clinical episodes of nephrotoxicity. Infections were seen in 6/22 (27%) patients: #3 (staphylococcal pneumonia), #5 (upper respiratory infection), #8 (*Aspergillus* in bronchoalveolar lavage), #9 (*Pseudomonas* infection of abdominal wound), #15 (*Clostridium difficile* colitis) and #21 (acute bronchitis).

Conventional core biopsies of the allograft were performed in 21 cases, and a fine needle aspiration biopsy in one case. Histopathological review of the core biopsies showed tubular vacuolization in 20/21 (95%), myocyte vacuolization in 15/21 (71%), arteriolar hyalinization in 7/21 (33%), striped fibrosis in 2/21 (10%) and glomerular capillary fibrin thrombi in 1/21 (5%) specimens, respectively. A minimal interstitial infiltrate involving less than 25% of the surface area was present in 11/21 (52%) biopsies. Rare foci of tubulitis (1–2 lymphocytes per tubular cross-section) were demonstrable in 4/21 (19%) cases. The needle aspiration specimen showed tubular vacuolization with no evidence of immune activation.

Discussion

Tacrolimus allograft nephrotoxicity is widely recognized, but to our knowledge, only one study has attempted to estimate its incidence in kidney transplant recipients (6). That investigation based the di-

agnosis of nephrotoxicity on the clinical course of the patient and graft biopsy, but the actual criteria used were not explicitly stated. It was found that renal toxicity was dependent on the dosing regimen and prior clinical experience with the drug. Thus, this study recorded a 44% incidence of nephrotoxicity when tacrolimus was administered at a dose of 0.3 mg/kg/d. Subsequently, with additional experience in the use of the tacrolimus a reduction in incidence to 20.5% was observed (6).

In the present study, we have observed a 17% incidence of nephrotoxicity in renal transplant biosies. The actual incidence of nephrotoxicity is probably higher, since tacrolimus dosage reduction is at times performed without a biopsy. The initial maintenance dose of tacrolimus in our patients was 0.15 mg/kg twice daily. The ultimate maintenance dose, which was fine tuned by serial determinations of plasma or whole-blood levels of tacrolimus, varied in different patients. It is important to stress that the incidence of nephrotoxicity reported here refers to the use of tacrolimus as a primary immunosuppressant after renal transplantation. In patients receiving intravenous tacrolimus as "rescue" therapy for refractory renal or hepatic allograft rejection, initial nephrotoxicity is seen in nearly all patients (19–21). The definition of nephrotoxicity used in this study required a fall in creatinine in response to reduction in the maintenance dose of tacrolimus. Hence, only reversible episodes of tacrolimus nephrotoxicity were identified. Other investigators have described patients with apparently persistent nephrotoxicity (6, 10). However, it is not always clear whether the clinically non-responsive cases sustained additional adverse effects such as dehydration, acute tubular necrosis, drug reactions or transplant glomerulopathy to explain the persistent graft dysfunction. Progressive drug induced renal dysfunction may occur in patients receiving continuous tacrolimus immunosuppression, since the nephrotoxic and anti-rejection actions of this drug are mechanistically related (22). However, recognition and distinction of such insidiously developing toxicity from chronic rejection is difficult on clinical grounds. Chronic tacrolimus nephrotoxicity could be better studied in liver transplant recipients without the confounding influence of chronic rejection. However, these patients are predisposed to renal dysfunction caused by sepsis, hypotension, hepato-renal syndrome, and glomerulopathy associated with liver disease, all of which would need to be distinguished from tacrolimus nephrotoxicity. Studies of chronic tacrolimus toxicity in heart and lung transplant recipients should likewise control for elevations in serum creatinine due to nephrotoxic antibiotics and congestive heart failure existing at the time of transplantation or developing subsequently.

Nephrotoxicity episodes were associated with elevated plasma or whole-blood in tacrolimus levels in 18/22 patients. In other investigations, good correlation between blood tacrolimus levels and graft dysfunction have been observed by some authors (23, 24), but not by others (11, 25). The percent dose reduction necessary to restore allograft function varied, reflecting the known variability of tacrolimus pharmacokinetics in individual patients (26). Drug interactions appeared to modify further the disposition of tacrolimus in three cases. Thus, case 8, which required the greatest dose reduction (89%), was receiving itraconazole, a drug known to compete with tacrolimus for metabolism by the hepatic microsomal cytochrome P450 system (27). Inhibition of tacrolimus detoxification by itraconazole would explain why this patient required such a drastic reduction in dose, and showed a lag period of 14 d before reversal of nephrotoxicity could be observed clinically. Diltiazem, another drug biotransformed by the liver microsomes (28), was used in patient #10, who required a 66% dose reduction in tacrolimus. An extremely high level of whole-blood tacrolimus (50.5 ng/ml) was recorded in case 5, who received clarithromycin, a macrolide antibiotic structurally related to both erythromycin and tacrolimus. Interactions between clarithromycin and tacrolimus have not been previously observed to the best of our knowledge, but erythromycin is known to inhibit competitively the metabolism of tacrolimus by the cytochrome P-450 system. We have previously reported a kidney transplant recipient in whom the plasma Tacrolimus level increased from 1.3 to 8.5 ng/ml within 4 d of starting erythromycin (29).

The reported incidence of hyperkalemia in Tacrolimus treated kidney transplant patients varies from 27 to 67% (6, 10, 19, 30–32). Its specific incidence in patients with nephrotoxicity is not mentioned in these studies. In the current study, one or more values of elevated serum potassium occurred in 9/22 (41%) cases with renal dysfunction. Hyperkalemia as an isolated finding without other evidence of impaired kidney function has been described in 9% of patients (31). The mechanisms responsible for hyperkalemia are not well understood, but an effect of tacrolimus on mineralocorticoid secretion and altered mineralocorticoid activity at the renal tubules have been proposed. Clinically, hyperkalemia induced by Tacrolimus usually responds readily to dietary restriction, potassium binding resins and fludrocortisone.

Altered glucose metabolism is another recognized toxicity of Tacrolimus. Changes in the peripheral sensitivity to insulin and/or response of islet cells to blood glucose lead to hyperglycemia in 25–35% of transplanted subjects (24, 30). Post-trans-

plant diabetes mellitus defined as persistently high blood sugar with an abnormal glucose tolerance test is seen in 4–22% of patients (2, 30, 33, 34). Evaluation of this side effect was difficult in 11 of our cases with known insulin-dependent diabetes mellitus, since by definition these subjects were hyperglycemic even before they received Tacrolimus. Considering only patients transplanted for diseases other than diabetes, 4/11 patients with Tacrolimus nephrotoxicity had hyperglycemia defined as blood glucose exceeding 7.7 mmol/l (140 mg/dl) on at least three occasions (35). Intravenous methylprednisolone had been administered empirically to one patient while the result of an allograft needle biopsy was pending. The remaining 3 patients were on stable maintenance doses of steroids, and the hyperglycemia was likely a manifestation of Tacrolimus toxicity.

In summary, this study has shown that reversible Tacrolimus nephrotoxicity accounts for 17% of renal allograft dysfunction episodes investigated by needle biopsy. The diagnosis of Tacrolimus nephrotoxicity was based on rigorous criteria, namely a rise in serum creatinine requiring biopsy, absence of histopathologic changes of acute rejection, and clinical response to reduction in the dose of Tacrolimus. It was noted that Tacrolimus toxicity could occur both early and late post-transplant. Plasma or whole-blood Tacrolimus levels were typically high at the time of clinical diagnosis, and the peak Tacrolimus level preceded the peak in serum creatinine. A reduction in dosage led to an improved serum creatinine within 1–14 d. Hyperkalemia and hyperglycemia were noted in several cases during the episodes of nephrotoxicity.

Acknowledgments

This work was supported by the Pathology Education & Research Foundation, Pittsburgh, PA, and has been presented in abstract form at the International Transplantation Society Meeting at Barcelona, Spain, August, 1996.

References

- SHAPIRO R, JORDAN M, SCANATLEBURY V, et al. Renal transplantation at the University of Pittsburgh: the impact of FK506. In: TERASAKI PI and CECKA JM, eds. *Clinical Transplants*. Los Angeles: UCLA Tissue Typing Laboratory, 1994, pp. 229–236.
- SHAPIRO R, JORDAN ML, SCANTLEBURY V, et al. A prospective randomized trial of FK506-based immunosuppression after renal transplantation. *Transplantation* 1995; 59: 485.
- JORDAN ML, SHAPIRO R, VIVAS CA, et al. FK506 "rescue" for resistant rejection of renal allografts under primary cyclosporine immunosuppression. *Transplantation* 1994; 57: 860.
- Japanese FK506 Study Group. Japanese study of FK506 on kidney transplantation: Results of an early phase II study. *Transpl Proc* 1991; 23: 3071.
- GIERTSON D, CECKA JM, TERASAKI PI. The relative effects of FK506 and cyclosporine on short- and long-term kidney graft survival. *Transplantation* 1995; 60: 1384.
- OCHIAI T, ISHIBASHI M, FUKAO K, et al. Japanese multicenter studies of FK506 in renal transplantation. *Transpl Proc* 1995; 27: 50.
- Japanese FK506 Study Group: Clinicopathological evaluation of kidney transplants in patients given a fixed dose of FK506. *Transpl Proc* 1991; 23: 3111.
- PLATZ K, MUELLER AR, BLUMHARDT G, et al. Nephrotoxicity following orthotopic liver transplantation. *Transplantation* 1994; 58: 170.
- European FK506 Multicentre Liver Study Group. Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. *Lancet* 1994; 344: 423.
- ALESSIANI M, CILLO U, FUNG J, et al. Adverse effects of FK506 overdosage after liver transplantation. *Transpl Proc* 1993; 25: 628.
- PORAYKO MK, TEXTOR SC, KROM RAF, et al. Nephrotoxic effects of primary immunosuppression with FK506 and cyclosporine regimens after liver transplantation. *Mayo Clin Proc* 1994; 69: 105.
- KEENAN RJ, KONISHI H, KAWAI A, et al. Clinical trial of Tacrolimus versus cyclosporine in lung transplantation. *Ann Thorac Surg* 1995; 60: 580.
- ARMITAGE JM, KORMOS RL, MORITA S, et al. Clinical trial of FK506 immunosuppression in adult cardiac transplantation. *Ann Thorac Surg* 1992; 54: 205.
- MCDIARMID SV, COLONNA JO, SHAKED A, AMENT ME, BUSUTTLIL RW. A comparison of renal function in cyclosporine and FK506 treated patients after primary orthotopic liver transplantation. *Transplantation* 1993; 56: 847.
- MUELLER AR, PLATZ KP, BLUMHARDT G, et al. The superior immunosuppressant according to diagnosis: FK506 or cyclosporine A. *Transpl Proc* 1995; 27: 1117.
- TEXTOR SC, WIESNER R, WILSON DJ, et al. Systemic and renal hemodynamic differences between FK506 and cyclosporine in liver transplant recipients. *Transplantation* 1993; 55: 1332.
- JAIN AB, ABU-ELMAGD K, ABDALLAH H, et al. Pharmacokinetics of FK506 in liver transplant recipients after continuous intravenous infusion. *J Clin Pharmacol* 1993; 33: 606.
- JAIN AB, PINNA A, FUNG JJ, et al. Capillary blood versus arterial or venous blood for tacrolimus monitoring in liver transplantation. *Transplantation* 1995; 60: 512.
- JORDAN ML, SHAPIRO R, VIVAS C, et al. FK506 rescue for resistant rejection of renal allografts under primary cyclosporine immunosuppression. *Transplantation* 1994; 57: 860.
- HEBERT MF, ASCHER NL, LAKE JR, ROBERTS JP. Efficacy and toxicity of FK506 for the treatment of resistant rejection in liver transplant patients. *Transpl Proc* 1991; 23: 3109.
- DEMETRIS AJ, FUNG JJ, TODO S, et al. Conversion of liver allograft recipients from cyclosporine to FK506 immunosuppressive therapy- A clinicopathologic study of 96 patients. *Transplantation* 1992; 53: 1056.
- PETERS DH, FITTON A, PLOSKER GL, FAULDS D. Tacrolimus. A review of its pharmacology, and therapeutic potential in hepatic and renal transplantation. 1993; *Drugs* 4: 746.
- ABU-ELMAGD K, FUNG JJ, ALESSIANI M, et al. The effect of graft function on FK506 plasma levels, dosages, and renal function, with particular reference to the liver. *Transplantation* 1991; 52: 71.
- TAKAHARA S. Efficacy of FK506 in renal transplantation. *Ann N Y Acad Sci* 1993; 696: 235.

25. MCCAULEY J, FUNG J, JAIN A, TODO S, STARZL TE. The effects of FK506 on renal function after liver transplantation. *Transpl Proc* 1990; 22: 17.
26. VENKATARAMANAN R, JAIN A, WARTY VS, et al. Pharmacokinetics of FK506 in transplant patients. *Transpl Proc* 1991; 23: 2736.
27. PRASAD TNV, STIFF DD, SUBBOTINA N, et al. FK506 (Tacrolimus) metabolism by rat liver microsomes and its inhibition by other drugs. *Res Commun Chem Pathol Pharmacol* 1994; 84: 35.
28. IWASAKI K, MATSUDA H, NAGASE K, SHIRAGA T, TOKUMA Y, UCHIDA K. Effects of twenty-three drugs on the metabolism of FK506 by human liver microsomes. *Res Commun Chem Pathol Pharmacol* 1993; 82: 209.
29. JENSEN C, JORDAN M, SHAPIRO R, et al. Interaction between tacrolimus and erythromycin. *Lancet* 1994; 344: 825.
30. FUNG JJ, ALESSIANI M, ABU-ELMAGD K, et al. Adverse effects associated with the use of FK506. *Transpl Proc* 1991; 23: 3105.
31. REDING R, WALLEMACQ PE, LAMY ME, et al. Conversion from cyclosporine to FK506 for salvage of immunocompromised pediatric liver allografts. *Transplantation* 1994; 57: 93.
32. The U.S. Multicenter FK506 Liver Study Group. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression in liver transplantation. *N Engl J Med* 1994; 331: 1110.
33. JINDAL RM. Posttransplant diabetes mellitus-A review. *Transplantation* 1994; 58: 1289.
34. SCANTLEBURY V, SHAPIRO R, FUNG J, et al. New onset of diabetes in FK506 vs. cyclosporine-treated kidney transplant recipients. *Transpl Proc* 1991; 23: 3169.
35. ROTH D, MILGROM M, ESQUENAZI V, FULLER L, BURKE G, MILLER JS. Post-transplant hyperglycemia. *Transplantation* 1989; 47: 278.