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Use of FK 506 in Pediatric Patients

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FK 506 is an immunosuppressive drug that holds particular promise for pediatric patients because of its potency, relatively low toxicity, and simplicity of administration.[1,2] Above all advantages is elimination of the need for adjuvant steroid therapy in the majority of cases. It was introduced for clinical trials in pediatric patients in September 1989. We report here our total experience with FK 506 in pediatric recipients of commonly transplanted organs up to May 1, 1990 with follow-up to August 1, 1990. In addition, experience with new applications of FK 506 is included. A total of 74 pediatric patients were treated for the diverse indications summarized in Tables 1 to 4.

THERAPEUTIC PRINCIPLES

When needed IV, the FK 506 dose was 0.15 mg/kg/d given as a slow IV infusion. The starting oral dose was 0.15 mg/kg twice per day. At the time of conversion from IV to oral dosing, one day of overlap was usually allowed.[1-4]

Prednisone was administered at 20 mg/d for heavier children or 10 mg/d for patients lighter than 10 kg. The steroids were rapidly tapered and discontinued when the graft function was stable. Augmented FK 506, increased steroids, or OKT3 were given if rejection occurred.

LIVER TRANSPLANTATION

Primary Liver Transplantation

Thirty patients underwent liver transplantation for the first time under FK 506 (Table 1). Three died. The deaths were due to tension hemothorax after a central venous line placement intraoperatively (1 case), nonreversal of hepatic coma (1 case) and cytomegalovirus (CMV) pneumonitis (1 case). Three of the children required retransplantation, two for hepatic artery thrombosis and one for primary graft dysfunction. Updated clinical data are shown in Table 1. At 90 days posttransplant, 21 (77.7%) of the patients are steroid free and the average daily prednisone dose for the whole surviving group is 0.83 mg/d (Table 1). The rate of removal from prednisone is shown in Fig 1.

Liver Transplant Rescue

Twenty-six patients who had either early or late rejections on conventional immunosuppression were treated with FK 506 as described elsewhere.[4,5] Three of these patients died of systemic fungal infection (one case), multifocal bronchopneumonia complicating cystic fibrosis (one case), and tracheostomy failure and respiratory arrest after retransplantation.

Seven of these 26 patients required retransplantation, but in five of the seven examples, the patients were placed on FK 506 at the time of retransplantation after conventional therapy had failed.

Table 1. Pediatric Liver Transplantation

	Primary	Rescue
No.	30	26
Age (y, mean)	4.2	8.7
Follow-up (d, mean)	150	150
Mortality	3	3
Retransplantation	3	7*
Current FK 506 dose (mg/kg/d, orally)	0.33	0.24
Current prednisone dose (mg/d)	0.83	1.6
Patients on/off prednisone	6/21	7/16
No. of patients on antihypertensive medications	0	8†
Total bilirubin (mg/dL)	0.4	0.46‡
SGOT (IU)	77	79‡
BUN (mg/dL)	20	24§
Creatinine (mean)	0.5	0.92

Abbreviations: SGOT, serum glutamic-oxalocetic transaminase; BUN, blood urea nitrogen.
*Five patients were placed on FK 506 at the time of retransplantation.
†Fifteen patients were on antihypertensive medications before rescue.
‡Mean total bilirubin, SGOT before rescue: 4.7 mg/dL, 395 IU.
§Mean BUN, creatinine before rescue: 23 mg/dL, 0.8 mg/dL.

Relevant clinical data are shown in Table 1. Steroids have been stopped in 16 of the 23 surviving patients; many were steroid toxic previously because of efforts with augmented prednisone doses to retain the grafts.

HEART TRANSPLANTATION

Primary Heart Transplantation

Seven primary heart transplant recipients were treated with FK 506.[6,7] The only death was of a patient who was severely immunocompromised from lymphocyte depletion and protein-losing enteropathy, a complication of a previous Fontan operation for tricuspid atresia. The patient also had severe preexisting lung disease. Multiple opportunistic infections developed 2 months posttransplantation.

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Supported by research grants from the Veterans Administration and project grant no. DK 29961 from the National Institutes of Health, Bethesda, MD.

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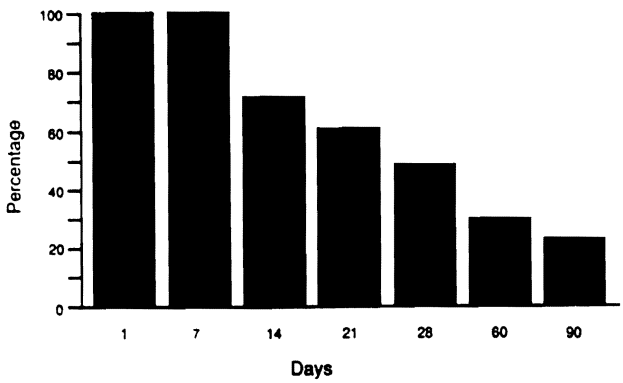

Fig 1. Percentage of pediatric patients on steroids after primary liver transplantation under FK 506.

Heart Transplant Rescue

Three patients who suffered intractable rejection on conventional drug therapy were switched to FK 506.[7] One of these patients was rejecting her second graft 6 months after retransplantation, which was necessitated by chronic rejection of her first graft over a period of 7 years. All three patients had a good result with clinical improvement and an improvement in endomyocardial biopsies. Their cushingoid appearance was relieved as steroids were reduced or stopped.

KIDNEY TRANSPLANTATION

A 13-year-old patient underwent primary kidney transplantation on FK 506 for end-stage renal disease due to hemolytic uremic syndrome (HUS).[8,9] There has been no evidence of recurrent disease in the transplanted kidney. HUS, at least when it is a complication of cyclosporine (CyA), responds to FK 506.[10] Renal function is satisfactory (Table 2).

HEART-LIVER TRANSPLANTATION: FK 506 FOR THE TREATMENT OF THE FAILING LIVER GRAFT

A 6-year-old patient who underwent heart and liver transplantation in 1984[11] developed chronic rejection and non-A non-B hepatitis in the liver graft. Liver function improved initially after switching from CyA to FK 506. Later, worsening of the non-A non-B hepatitis necessitated liver replacement in February 1990. She has developed recurrent non-A non-B hepatitis in her second liver graft but is clinically well with good liver function under treatment with interferon alpha (IFN-α)[12] (Table 2). She has never had a cardiac rejection and has a normal recent coronary angiogram. The reason for the heart-liver transplantation was homozygous type 2 hyperlipidemia. The serum cholesterol has been lower with FK 506 than at any time previously (see footnote, Table 2).

LIVER AND ISLET PRIMARY TRANSPLANTATION

Two patients with extensive hepatic malignancies and regional metastases were treated with upper abdominal exenteration[13,14] followed by liver and pancreatic islet transplantation. One patient died, of tumor recurrence 5 months after transplantation. The other patient is well, without any evidence of recurrence, and with normal liver function (Table 3). She is insulin free, and is the first unambiguous example of a human successful pancreatic islet transplantation.[15,16]

INTRACTABLE CHRONIC GRAFT VS HOST DISEASE

Two patients were referred to us with severe chronic graft vs host disease 6 months following bone marrow trans-

Table 2. FK 506 in Pediatric Extrahepatic Transplantation

	Heart		Kidney	Heart-Liver
	Primary	Rescue	Primary	Rescue
No.	7	3	1	1
Age (y, mean)	7.8	16.4	13	13
Follow-up (d, mean)	162	176	100	270
Mortality	1	0	0	0
Retransplantation	0	0	0	1
Current FK 506 dose (mg/kg/d, orally)	0.22	0.25	0.18	0.28
Current prednisone dose (mg/d)	0	4	10	0
Patients on/off prednisone	2/4	3/0	NA	NA
No. of patients on antihypertensive medications	0	0*	1	0
Total bilirubin (mg/dL)	0.28	0.20	0.2	0.7†
SGOT (IU)	20	51	16	79
BUN (mg/dL)	23	34.5	38	36
Creatinine (mg/dL)	0.76	1.5	1.8	1.0

*Two patients on antihypertensive medications before rescue.
†Serum cholesterol before/after rescue: 491 mg/dL/183 mg/dL.

Table 3. FK 506 in New Transplant Applications

	Liver-Pancreatic Islet*	GVHD, After Bone Marrow Transplantation		Liver-Intestine
No.	2	2		1
Age (y, mean)	15,7	8	9	3
Follow-up (d, mean)	180 (died) 220	90	90	21
Mortality	1	0		0
Current FK 506 dose (mg/kg/d, orally)	0.12	0.4	0.23	0.06 (IV)
Current prednisone dose (mg/d)	0	10	0†	0
No. of patients on antihypertensive medications	0	0	0	0
Total bilirubin (mg/dL)	0.4	1.7	0.8‡	0.4
SGOT (IU)	29	84	99§	14
BUN (mg/dL)	2	25	23‖	52
Creatinine (mg/dL)	0.7	0.5	1.8¶	1.5

*Pancreatic islet function: the patient is insulin free. Fasting and nonfasting blood sugar: 98 mg/dL, 105 mg/dL; basal and peak C-peptide: 0.96, 2.8; exogenous insulin: 0.
†Prednisone dose before FK 506 rescue: 150 mg/d, 90 mg/d, respectively.
‡Total bilirubin before rescue: 6.3 mg/dL (patient 1), 13.8 mg/dL (patient 2).
§SGOT before rescue: 113 IU (patient 1), 411 IU (patient 2).
‖BUN before rescue 3-mg/dL (patient 1), 22 mg/dL (patient 2).
¶Creatinine before rescue 0.1 mg/dL (patient 1), 0.2 mg/dL (patient 2).

plantation for leukemia under conventional immunosuppression. Both had skin, intestinal, and hepatic involvement. High dose FK 506 was used at first, with oral doses that peaked at more than 1.0 mg/kg/d (more than three times the usual).

The first patient had a gradual but steady improvement on FK 506 and was discharged and sent home in 4 weeks in good condition. Steroids were tapered rapidly and discontinued on discharge from the hospital.

The second patient's symptoms persisted for 2 months and then gradually resolved during the third month of FK 506 treatment. The patient is still receiving 10 mg/d of prednisone.

In both cases, the response could be monitored objectively by the slow resolution of jaundice (Table 3, see footnote).

FOCAL SCLEROSING GLOMERULONEPHRITIS

A patient with biopsy proven focal sclerosing glomerulonephritis was started on FK 506 in November 1989 because of the nephrotic syndrome, which was refractory for 13 months to continuous treatment with high doses of prednisone and intermittent treatment with other conventional agents including cyclophosphamide. As reported elsewhere,[17] a complete remission was promptly achieved at the same time as steroid therapy was stopped (Table 4).

LIVER-INTESTINE TRANSPLANTATION

A 3-year-old child, who had liver failure and the short gut syndrome secondary to perinatal necrotising enterocolitis and chronic IV alimentation, received a liver and complete small bowel. She has normal liver function (Table 3). The ileostomy stoma, which appears normal, has had minimal evidence of rejection on biopsy. This case is included in the present report because of its intrinsic interest, and is the only one treated after the cut-off date of May 1, 1990. Her follow-up is only 3 weeks.

ADVERSE REACTIONS

Adverse effects are being monitored systematically through clinical observation and collection of questionnaires that are given periodically to the patients and/or their parents.

Several toxicity reports have been published or are being given at this meeting.[18-23] The side effects in children are similar to those in adults.

In our 74 patients, there were four fatal infections: two in liver rescue patients, one in a primary heart transplant

Table 4. FK 506 in the Treatment of Autoimmune Disease: Rescue Treatment of Focal Sclerosing Glomerulonephritis, a Case Report

Age: 30 mo Follow-up: 6 mo	Before	After
Edema	+++	0
Diuretics	2	0
Urine protein (mg/d)	1406	0
Serum cholesterol (mg/dL)	630	146
Creatinine clearance (mL/min/1.73 m^2)	82.0	87
Serum creatinine (mg/dL)	0.3	0.3
BUN (mg/dL)	6	6
Total bilirubin (mg/dL)	0.5	0.4
SGOT (IU/L)	12	25

Note. Current FK 506 dose: 0.20 mg/kg/d; current prednisone dose: 0 mg/d; Pre-FK 506 prednisone dose: 35-70 mg/d.

patient, and one in a primary liver patient. Three of the four patients were immunocompromised when switched to or started on FK 506. There has been one example of lymphoproliferative disease of the stomach on a liver rescue patient that disappeared after a reduction of the immunosuppression.

Nonimmunologic side effects of FK 506 are similar to those of CyA and include nephrotoxicity, neurotoxicity, and diabetogenicity.[24] De novo development of diabetes mellitus was observed in two liver rescue patients: one later became insulin independent after steroid withdrawal and reduction of the FK 506 dosage. The second patient still requires insulin treatment. Similar events have been reported in adults undergoing liver rescue.[18]

Neurologic complications such as those reported in adults[23] have not yet been seen in infants and children. Transient renal dysfunction has developed mainly in liver rescue patients and also in the heart transplant recipients during the first 2 weeks after transplantation. Inappropriately high IV doses of FK 506 were thought to have been given as a management policy during this learning state of the trials.[19]

CONCLUSION

FK 506 appears to be the most effective immunosuppressive agent available today for the treatment of infants and children. Its use should allow improvement in graft and patient survival, as well as allowing an improved quality of steroid-free growth and development. Previously impractical kinds of transplantations should be made easier, and it may be possible to expand this technology to the more widespread treatment of autoimmune disorders in the pediatric population.

REFERENCES

1. Starzl TE, Todo S, Fung J, et al: Lancet 2:1000, 1989
2. Todo S, Fung JJ, Starzl TE, et al: Ann Surg:212, 295, 1990
3. Venkataramanan R, Jain A, Cadoff E, et al: Transplant Proc 22:52, 1990
4. Fung JJ, Todo S, Tzakis A, et al: Transplant Proc 23:(this issue), 1991
5. Fung JJ, Todo S, Jain A, et al: Transplant Proc 22:6, 1990
6. Armitage JM, Kormos RL, Fung J, et al: Transplantation (in press)
7. Armitage JM, Kormos RL, Griffith BP, et al: Transplant Proc 23:(this issue), 1991
8. Starzl TE, Fung J, Jordan M, et al: JAMA 264:63, 1990
9. Shapiro R, Jordan M, Fung J, et al: Transplant Proc 23:(this issue), 1991
10. Mccauley J, Bronsther O, Fung J, et al: Lancet 2:1516, 1989
11. Starzl TE, Bilheimer DW, Bahnson HT, et al: Lancet 1:1382, 1984
12. Davis GL, Balant LA, Schiff ER, et al: N Engl J Med 321:1501, 1989
13. Starzl TE, Todo S, Tzakis A, et al: Ann Surg 210:374, 1989
14. Tzakis AG, Todo S, Starzl TE: Transplant Proc 22:273, 1990
15. Alejandro R, Tzakis A, Ricordi C, et al: Transplant Proc 23:(this issue), 1991
16. Tzakis AG, Ricordi C, Alejandro R, et al: Lancet 336:402, 1990
17. Mccauley J, Tzakis AG, Fung JJ, et al: Lancet 335:674, 1990
18. Mieles L, Gordon RD, Mintz D, et al: Transplant Proc 23:(this issue), 1991
19. Abu-Elmagd K, Fung JJ, Alessiani M, et al: Transplantation (in press)
20. McCauley J, Takaya S, Fung J, et al: Transplant Proc 23:(this issue), 1991
21. Shapiro R, Fung JJ, Jain A, et al: Transplant Proc 22:35, 1990
22. Kusne S, Martin M, Shapiro R, et al: Transplant Proc 23:(this issue), 1991
23. Reyes J, Gayowski T, Fung J, et al: Transplantation (in press)
24. Starzl TE, Fung JJ, Todo S: JAMA 263:2686, 1990