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Two-Year Experience With FK 506 in Pediatric Patients

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The entire pediatric experience with FK 506 between September 1989, when the drug was introduced at Children's Hospital of Pittsburgh, and October 1991 is presented. Follow-up is to August 1, 1992.

THERAPEUTIC PRINCIPLES

The starting dose of FK 506 has been kept the same in the pediatric population as when the drug was introduced: 0.15 mg/kg/d IV as a continuous infusion and 0.15 mg/kg bid orally.[1] The dose was increased in case of rejection if the trough serum FK 506 level was <2 ng/mL and there was no nephrotoxicity. The dose was decreased in the absence of rejection if the serum FK 506 level was >3 ng/mL or if there was nephrotoxicity.

The doses, including starting dose, were lower in the presence of liver dysfunction, as in liver rescue attempts.

Prednisone

Prednisone was administered at 20 mg/d for larger children or 10 mg/d for smaller children (<10 kg body weight). It was tapered and then discontinued when the graft function was stable. In kidney and intestinal transplantation, prednisone starting at 200 mg/d for larger children and 100 mg/d for smaller children was used. The dose was tapered to 20 mg/d and 10 mg/d, respectively, within 5 days.

Freedom from Steroids

Of 147 patients who received primary transplantation, and are alive with functioning grafts, 126 (86%) are steroid-free (93% of liver recipients, 41% of cadaveric kidneys, 71% of living related, 82% of heart, 33% of lung, 75% of liver-intestine, 100% of solitary intestine). Of 57 patients whose grafts were successfully rescued, 40 (70%) are steroid-free (liver 82%, kidney 20%, heart 100%, lung 100%).

Azathioprine

Courses of azathioprine (1 to 2 mg/kg/d) were used as supplemental immunosuppression mainly in cases of renal impairment. Twelve primary transplant recipients (2 liver, 1 liver intestine, 1 solitary intestine, 4 kidney, 2 heart, 2 lung) are receiving azathioprine (1 mg/kg/d) long term. In the rescue group, only two patients (liver recipients) are receiving azathioprine long term.

OKT3 was used on five occasions for the treatment of steroid-resistant rejection.

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Toxicity

Nephrotoxicity was similar to that observed with cyclosporine (CyA).[2] No patient required long-term dialysis.

Five children developed diabetes mellitus which receded spontaneously in four.[3] One child (liver transplant rescue) is receiving insulin long term.

Five patients developed posttransplantation seizures, which were resolved with medical treatment and dose reduction if the FK 506 level exceeded 2 ng/mL.

Lymphoproliferative Disease

Sixteen patients developed this complication[4]: 7 primary liver recipients, 1 liver rescue, 2 primary cadaveric kidney recipients, 1 living related kidney recipient, 1 primary heart, 1 lung, 1 lung rescue and 2 liver-small bowel transplant recipients.

Thirteen of them are alive and well with the existing grafts after dose reduction and acyclovir treatment. Three patients died: 1 liver transplant recipient after retransplantation, 1 primary heart, and 1 liver-small bowel transplant recipient.

Results in Different Groups—Primary Transplantation (Table 1)

Liver—One hundred sixteen patients received 128 grafts; of those, 100 patients (86%) are alive with normal liver function.[1, 2]

In six patients, the immunosuppression was completely discontinued because of lymphoproliferative disease (n = 4), recurrent infection (n = 1), or recurrent hepatitis (n = 1). They remain well with no evidence of rejection 6 to 20 months after immunosuppression was discontinued.

Combined Liver–Small Intestine—Six patients with combined intestinal and liver failure were treated with a combined liver–intestinal transplant. Four are alive with normally functioning grafts and no parenteral treatment. Two patients died: 1 of GVHD (a result of reduction of immunosuppression to combat peritonitis secondary to an anastomotic intestinal leak) and 1 of lymphoproliferative disease.[5,6]

Solitary Small Intestine—Three patients received a solitary intestine graft for treatment of intestinal failure, two after October 1991, but are included here because of their special interest. All patients are alive, well, and free of any parenteral therapy.[5,6]

Liver–Pancreatic Islets—Of two patients who received liver–pancreatic islets after upper abdominal exenteration for extensive malignancy, one died 5 months after transplantation of tumor recurrence.[7] The other patient is alive, tumor-free, and insulin-free 31 months after transplantation. This patient represents the first unequivocally successful case of islet transplantation.

Kidney (Cadaveric)—Thirteen transplants were performed on 13 patients: 3 were a second and 1 was a third transplant.[8] All patients are alive, and all but 2 have normally functioning grafts: 1 patient has recurrent membranoproliferative glomerulonephritis and impaired graft function, and the second patient lost his graft to recurrent hemolytic uremic syndrome.

Kidney (Living Related Donor)—Seven such transplants were performed.[9] No patient or graft was lost in this group. All patients have normally functioning grafts.

Heart—Twenty-one heart transplants were performed with 81% patient and graft survival. Mortalities (n = 4) were due to opportunistic infections (n = 3) and lymphoproliferative disease (n = l).[10]

Lung—Four patients received double-lung transplantation either in combination with heart (n = 1) or without (n = 3). One of these patients died of *Aspergillosis.* The surviving patients have normal graft function.

Rescue Therapy

Table 2 refers to rescue attempts to patients with liver, kidney, heart, or lung transplants failing under conventional immunosuppression. Of the liver patients, one was a liver–heart recipient. The patient required liver transplantation after attempted rescue[1] and died of unsuspected heart rejection 9 months later. Three of the patients were converted to FK 506 at the time of retransplantation. One of them also received a cadaveric kidney transplant at the same time. Of the kidney rescue patients,[11] five patients had acute rejection. Their rescue attempt was successful. Two patients had proteinuria due to chronic rejection and lost their grafts. One heart rescue patient died of acute rejection 11 months after conversion to FK 506. Initial postrescue biopsies showed resolution of the persistent acute rejection, which prompted the switch. Poor patient compliance or suicide is suspected in this case.[10]

Chronic GVHD Following Bone Marrow Transplantation

Five such patients were treated[12]: 2 responded to treatment, 1 patient required liver transplantation and is alive and well 15 months later, 1 died of pulmonary failure due to GVHD, and the remaining patient has an equivocal response.

Nephrotic Syndrome (Nontransplant)

Nine patients were treated.[13] All patients are alive, 5 of them (55%) had a favorable response. Advanced renal insufficiency or rapidly rising serum creatinine before treatment were the most significant prognostic indicators.

CONCLUSION

Increasing experience with FK 506 confirms our earlier favorable impression of its use in pediatric patients. It can be used virtually without steroids in the treatment of recipients of conventional transplants. It is efficacious in salvaging patients who failed conventional immunosuppression. It allows successful transplantation of previously forbidden organs, such as intestine and pancreatic islets. It can be effective in the treatment of nephrotic syndrome.

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Table 1

Two-Year Experience With FK 506 in Pediatric Patients: Primary Transplants

	Liver*	Kidney (Cadaver)	Kidney (LRD)	Heart	Lung	Liver + Islets	Liver–Small Bowel	Isolated Small Bowel
No	116	13	7	21	4	2	6	3
Age	2 mo–16 y	3–16 y	8–17 y	7 h–18 y	4–15 y	8 y, 16 y	6 mo–3 y	14 mo–10 y
Follow-up: (mo)	10–34	11–32	11–23	12–33	10–12	31	13–26	5–9
Graft survival	78%	92%	100%	81%	75%	50%	66%	100%
Patient survival	86%	100%	100%	81%	75%	50%	66%	100%

*One patient recerved simultaneous kidney transplantation but died from hepatic artery thrombosis. One patient developed aplastic anemia after transplantation from fulminant hepatitis and underwent successful bone marrow transplantation.

Table 2

Rescue of Transplants Treated With Conventional Immunosuppression

	Liver	Kidney	Heart	Lung	Nephrotic Syndrome, Nontransplant
No	57	7	5	1	9
Age	9 mo–17 y	6–15 y	7–17 y	10 y	2.5–13 y
Follow-up (mo)	11–34	8–26	10–21	12	10–32
Graft survival	71%	72%	80%	100%	55% improved
Patient survival	82%	100%	80%	100%	100%