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Pediatric Renal Transplantation Under FK 506 Immunosuppression

C.W.B. Jensen, M.L. Jordan, F.X. Schneck, R. Shapiro, A. Tzakis, T.R. Hakala, and T.E. Starzl

RENAL transplantation (12 cadaveric and 4 living-related donors) was performed in 16 pediatric recipients (mean age 10.8 years) under FK 506 immunosuppression in combination with prednisone therapy. At a mean follow-up of 8.5 months, patient and graft survival rates are 100% and 94%, respectively. The only graft loss was due to recurrent hemolytic uremic syndrome (HUS) 4 days after transplantation. In the functioning grafts, the mean serum creatinine is 1.29 ± 0.38 mg/dL and the mean BUN is 26.0 ± 9.6 mg/dL. Seven patients are taking no prednisone, five are receiving 2.5 to 5 mg per day, and three are taking 10 to 15 mg per day.

There were a total of nine rejection episodes in six patients and these were all successfully reversed. Complications of transplantation included one patient each with cytomegalovirus (CMV), pyelonephritis, a seizure disorder and headaches; two patients each developed insulin-dependent diabetes mellitus, and a posttransplant lymphoma (PTLD). These results would suggest that FK 506 is a potent immunosuppressant when used in the pediatric age group. The use of FK 506 for the immunosuppression of pediatric renal transplant recipients would appear to have the advantage of allowing for steroid withdrawal in a significant number of patients, thereby minimizing the steroid-related complications of which the pediatric population is at particular risk.

MATERIALS AND METHODS

Sixteen renal transplants (12 cadaveric and 4 living related) were performed in 16 pediatric patients (7 females and 9 males, mean age 10.8 ± 3.7 years; range 3.3 to 16.2 years) between December 14, 1989, and July 9, 1991. Twelve of these cases were primary transplantations and four were retransplants. Follow-up in these patients ranged from 0.6 to 15.2 months (mean 8.5 months). All patients received FK 506 and prednisone as primary immunosuppression.

Two transplants were performed using pediatric en-bloc kidneys recovered from donors aged 6 months and 3 years, respectively. Excluding these pediatric donors, the mean donor age was 21.6 years (range 4 to 46 years). Mean cold ischemic time of the kidneys was 33.7 ± 6.6 hours (range 24 to 44 hours), excluding the four living-related donations.

Donor and recipient HLA-A, HLA-B, HLA-DR typing were performed in all cases, but intentional donor-recipient HLA matching was not carried out. Only one patient had four or more antigen matches. Nine of 16 (56%) transplants were done with 0–2 antigen matches, six (38%) had three antigen matches, and one had a four-antigen match. Multiple mismatches were common with 12 (75%) having three or more antigens mismatched. Two patients were considered to be highly sensitized with panel-reactive antibodies (PRA) of 97% and 100%, respectively. All other recipients had a PRA of less than 10%. Absolute criteria for transplantation were ABO compatibility and a negative lymphocytotoxic cross-match using current sera.

The immunosuppression consisted of FK 506 in combination with steroid therapy. FK 506 was started in the recovery room with a continuous IV infusion of 0.1 mg/kg total daily dose. Oral doses started at 0.15 mg/kg twice daily with an IV dose overlap of 12 to 24 hours. Steroid therapy consisted of 1 g of methylprednisolone in the operating room followed by a prednisone taper to 20 mg per day by postoperative day 6. Further reductions in prednisone therapy were usually made in decrements of 2.5 mg per day starting at the third week posttransplant.

Biopsy-confirmed rejection episodes were treated with one-half to 1 g of IV boluses of methylprednisolone with or without a prednisone recycle. Prednisone recycle consisted of a starting dose of 100 to 200 mg a day tapered to 20 mg over 6 days. A 5- to 10-day course of OKT3, 5 mg per day IV was instituted in cases of severe or steroid-resistant rejection.

RESULTS

Patient and Graft Survival and Function

The clinical characteristics of the 16 patients are summarized in Table 1. Patient survival is 100% with a follow-up of 1 to 15 months (mean 8.5 months). All grafts achieved primary function defined as clearance of creatinine in the immediate postoperative period with early diuresis. At present, 94% of the grafts are functioning. No patient with a functioning graft required dialysis from the postoperative period onward. The only graft loss occurred in a 4-year-old boy with HUS receiving a second transplant with a PRA of 97%. His first graft was lost 3 years earlier owing to recurrent HUS in the graft 10 days after transplantation. With this transplant, the patient's allograft had excellent initial function until his fourth postoperative day when he rapidly became anuric. The allograft biopsy demonstrated recurrent HUS, and the graft could not be salvaged despite thrombolytic therapy.

The mean serum creatinine (SCR) of the 15 functioning grafts is 1.29 ± 0.38 mg/dL and mean blood urea nitrogen (BUN) is 26.0 ± 9.6 mg/dL. The mean serum uric acid and cholesterol levels are 6.66 ± 1.87 mg/dL and 200 ± 54 mg/dL, respectively.

Immunosuppression

The daily maintenance doses of FK 506 and prednisone are shown in Table 1. FK 506 dosage was based on achieving

From the Division of Urology, Dept. of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania.

Address reprint requests to C.W.B. Jensen, MD, 4414 Presbyterian Hospital, Pittsburgh, PA 15213.

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Table 1. Clinical Characteristics of 16 Pediatric Transplant Patients Receiving FK 506

Patient No.	Transplant Date	Transplant No.	M/F	Age (y)	Rejection	Rejection No.	OKT3	BUN*	Cr*	FK* mg/d	Prednisone* mg/d (ng/mL)	FK* Level	Follow-up (months)
1	12/14/89	1	F	10	no	—	—	18	0.9	6	2.5	0.7	15.2
2	06/10/90	1	F	14	yes	2	yes	18	1.2	12	0	0.3	13.1
3	06/13/90	1	M	15	no	—	—	34	1.7	14	0	0.6	13.1
4	08/26/90	3	F	7	yes	2	yes	26	1.9	6	5	0.3	10.6
5	08/30/90	1	M	10	no	—	—	20	0.5	7	0	0.3	9.5
6	09/05/90	1	F	14	yes	1	no	15	1.3	6	2.5	0.4	10.4
7	09/19/90	1	M	15	no	—	—	34	1.8	8	0	0.4	9.9
8	10/10/90	2	F	12	yes	2	no	47	2.1	0†	10	0	9.7
9	11/04/90	2	F	12	yes	1	no	42	1.8	8	5	2.6	7.9
10	11/09/90	1	M	9	no	—	—	12	1.2	8	2.5	0.4	8.0
11	12/08/90	2	M	4	no	—	—	Lost	Graft	10	HUS	—	—
12	12/22/90	1	M	3	no	—	—	34	0.6	6	0	0.6	6.2
13	01/22/91	1	M	8	no	—	—	18	1.2	8	0	0.4	6.0
14	02/08/91	1	M	8	no	—	—	29	0.8	5	0	0.2	5.3
15	05/28/91	1	M	9	yes	1	no	35	1.2	10	10	1.4	1.6
16	07/09/91	1	F	16	no	—	—	20	1.1	12	15	1.5	0.6

*At last follow-up (mean 8.5 months).
†Patient on Imuran.

12-hour serum trough levels between 1 to 2 ng/mL. Azathioprine was not used in combination with FK 506. Currently, seven patients (47%) are taking no prednisone, five (33%) are taking 5 mg or less daily, and three patients (20%) are on 10–15 mg/d.

Rejection Episodes

One or more episodes of rejection occurred in 6 (38%) out of 16 grafts. There were a total of nine rejection episodes in these six patients. Six (67%) of the rejection episodes occurred within the first 30 days after transplantation and of these five (56%) occurred within the first 2 weeks. All rejection episodes responded to treatment (steroid in 7 cases, OKT3 in 2) and had a good outcome—that is, a decrease in serum creatinine with continued allograft diuresis. Seven of the nine rejection episodes were characterized as mild based on allograft biopsy results and a minimal rise in serum creatinine. Both episodes requiring treatment with OKT3 occurred within 14 days of transplantation in patients with 0% PRA and were successfully reversed.

Complications

One episode of seizures occurred in a 3-year-old male during intravenous induction therapy with FK 506. Seizures in this case were manifested as episodes of unresponsiveness, staring, and lip smacking. The patient was treated with phenobarbitol and discontinuation of IV FK 506. This problem has not recurred while the patient has been on oral FK 506 therapy. There were no other neurologic sequelae in this patient. The only other neurologic complication was headaches in one patient, which resolved when the oral FK 506 was decreased.

Insulin-dependent diabetes mellitus developed de novo 4 months posttransplantation in a 14-year-old patient with spina bifida on FK 506 monotherapy, after the treatment of a rejection episode with high-dose steroids. This patient also developed recurrent allograft pyelonephritis for which she has required hospitalization. This may have been related to the cause of her end-stage renal disease (ESRD) (chronic pyelonephritis with reflux) for which she had undergone a sigmoid colocystoplasty with bilateral ureteral implantation 6 months prior to transplantation. Six months posttransplantation, this patient developed abdominal pain. Radiological investigation and biopsy confirmed the presence of a pleomorphic lymphoma (PTLD). One hepatic and two lung lesions have resolved with high-dose intravenous acyclovir and cessation of her immunosuppression. With resolution of these lesions and the development of moderate rejection 2 months later, the patient resumed low doses of FK 506 and prednisone while receiving oral acyclovir. She currently has excellent graft function with a serum creatinine of 1.3 mg/dL and no evidence radiologically of her PTLD.

Another patient developed nodular densities in her lungs and lymphadenopathy posttransplantation. Although the investigations and biopsies failed to disclose the etiology of these lesions, a presumptive diagnosis of PTLD was made. After the cessation of FK 506 and prednisone and with the administration of intravenous acyclovir, there was complete resolution of these lesions. Currently, the patient is being maintained on oral acyclovir, FK 506, and prednisone, with stable graft function.

The only other episode of infection was CMV in a 12-year-old girl who presented 2 months after transplantation with fever and an increase in serum creatinine. CMV was diagnosed on a culture of the serum buffy coat and

was treated successfully with a 10-day course of ganciclovir.

DISCUSSION

Renal transplantation is the treatment of choice for many children with end-stage renal disease because of improvements in immunosuppressive drug regimens. Since these regimens rely on combination cyclosporine-prednisone therapy, they carry with them inherent steroid-related complications including cataracts, obesity, Cushing's syndrome, diabetes, infection, growth retardation, and avascular bone necrosis. Several studies in the pediatric population have demonstrated the efficacy of limiting steroid use in an effort to avoid steroid complications, particularly allowing improvement in catch-up growth.[1,2] The toxic effects of cyclosporine (CyA) in children are significant and include hirsutism (100%), hypertension (73%), fine tremor (34%), acute reversible nephrotoxicity (10%), and hyperuricemia with long-term CyA usage.[1,3]

FK 506, a product of the fungus *Streptomyces tsukubaensis*, has a chemical structure and cytosolic binding sites different from CyA.[4–7] Despite being 100 times more potent than CyA in vitro, FK 506 does share the neurotoxicity, nephrotoxicity, and diabetogenicity of CyA.[4,5] The neurotoxicity observed with the intravenous formulation (tremors, headaches, insomnia, parathesias, and a sensation of racing) is diminished with oral therapy, in which only 13% of patients report symptoms.[8]

In this study, 13% of patients developed neurotoxicity (seizures and headaches) and two patients had minor infections (recurrent pyelonephritis and CMV syndrome). The drug's potency has allowed for the discontinuation of, or a significant reduction in, prednisone therapy in 80% of the patients in this study. Additionally, hirsutism and gingival hyperplasia have not been noted in this study group and hyperuricemia was seen in only 53% of our patients. On the other hand, the development of one proven PTLD and one presumed PTLD and the development of insulin-dependent diabetes mellitus in two patients are significant deterrents to the usage of FK 506, despite the reversal of the two cases of PTLD and the discontinuation of insulin therapy with the termination of prednisone in the two patients with diabetes.

Our patient and graft survival rates of 100% and 94%, respectively, with a mean follow-up of 8.5 months, are encouraging. Significantly, the incidence of acute rejection was low (38%), early (67% occurred within the first month after transplantation), and mild (78%). All rejection episodes were reversed, including the two severe rejection episodes requiring OKT3 treatment. Nevertheless, 80% of our patients were on no prednisone (7 patients) or low dosages (5 patients: 2.5–5 mg/d) of prednisone, results noted in the adult population.[9] Therefore, it would appear that FK 506 is an effective form of immunosuppression in the pediatric renal transplant population. It appears to have the significant advantages of avoiding high-dose prednisone therapy and the specific CyA-related complications, which are both bothersome in the pediatric population. The development of one and possibly two post-transplant lymphomas, both reversed, is a concern that will need to be addressed, perhaps by dose reduction in certain patients.

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