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Early Infections in Kidney Transplant Recipients Under FK 506

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INFECTION remains a major cause of morbidity and mortality in transplant recipients. Sixty-six consecutive kidney transplants in 65 recipients were performed between September 1989 and June 3, 1990 using the experimental immunosuppressive agent FK 506. This report highlights the early infectious complications. The aims of this study were to determine the frequency of early infections in kidney recipients under FK 506, and to compare infections occurring in patients receiving a first renal allograft (primary) with those undergoing kidney retransplantation (secondary) using this new agent.

METHODS

Forty-one primary and 22 secondary retransplantation patients were followed prospectively. Three patients were excluded from evaluation due to cardiac death at 48 hours and arterial thrombosis and allograft loss at 24 hours, and one secondary patient who had received intense immunosuppression until the time of his retransplant was also excluded.[1] One patient is included in both primary and secondary retransplantation groups having been a failure from the primary series at 130 days.

Surveillance cultures were obtained in most patients. In eight cases of allograft loss, follow-up was terminated 7 days after nephrectomy. Routine prophylaxis included 1 g cefazolin IV every 8 hours for a total of three doses. Bactrim (80 mg trimethoprim/400 mg sulfamethoxazole) daily, 500 000 U oral mycostatin three times a day, and high dose acyclovir (800 mg four times a day) with doses adjusted according to renal function.

The immunosuppression protocol included FK 506 and steroids in all patients. A first IV dose of FK 506 at 0.15 mg/kg was given, usually in the recovery room, and an IV dose of 0.075 mg/kg dose was repeated every 12 hours until oral intake was resumed. Oral doses (0.15 mg/kg) were administered twice a day and these were increased when indicated by suspected rejection or reduced if drug toxicity was seen. Reduced doses were sometimes given once a day instead of every 12 hours. The first 25 patients received 1 g IV bolus of methylprednisolone intraoperatively. Prednisone was started at 200 mg on the first postoperative day and reduced in daily 40 mg steps to a maintenance dose of 20 mg by day 6. The remaining patients received low dose (20 mg/d) prednisone from the time of surgery. When possible, the steroid dose was tapered over the first several weeks and stopped. Supplementary steroids or OKT3 were given if persistent rejection was suspected clinically or diagnosed with biopsy.[2]

The diagnosis of infection was made using clinical and laboratory criteria as previously described.[3]

Proportions were analyzed with chi-square test and means were compared with Student's t test.

Table 1. Characteristics of Those Patients Undergoing Primary and Secondary Retransplantation under FK 506

	Primary	Secondary
Patients	41	22
Male/female	16/25	17/5
Mean age (y)	42 ± 14.5	36 ± 10.3
Range	10-72	18-63
Diabetes	13	5
Mean follow-up (d)	158 ± 78.6	147 ± 90.9

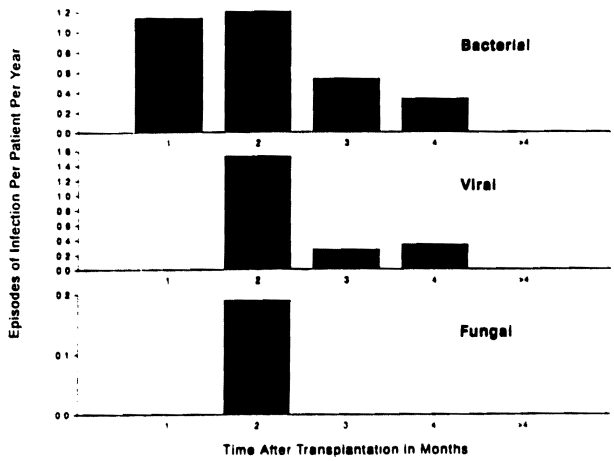

Fig 1. Incidence in episodes of infection per patients per year and time after kidney transplantation when infections occurred.

RESULTS

The study population is shown in Table 1 and included 41 primary and 22 secondary retransplantation patients. Diabetic nephropathy was the original diagnosis in 18 evaluable patients. Mean follow-up time was 152 days with 35 patients followed for more than 4 months. All infections occurred within 4 months with 81% seen within the first 60 days (Fig 1). No patient died from infection and no significant differences were seen in diabetics. The incidence of infections is shown in Table 2. These patients are compared with a group of 64 cyclosporine (CyA) patients reported from our institution in 1983.[2] Overall, 33% of FK 506 patients developed infection compared with 61% of the historical CyA patients. Twenty-six episodes of infection

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Table 2. Comparison of Infections Between CyA-Treated Patients in 1981-1982 (n = 64) and the FK 506 Patients, 1989-1990 (n = 63)

	CyA	FK 506
All infections		
Patients infected	61%	33%
Total episodes	63	26
Mean episodes	0.98	0.41
Nonviral infections		
Patients infected	41%	21%
Total episodes	39	16
Mean episodes	0.61	0.25
Infection related	—	—
Deaths/total deaths	0/1	0/0

were seen in 21 of 63 study patients. Lethal systemic sepsis was notably absent. Of 15 bacterial infections, 8 (53%) originated in the urinary tract and were mild, with bacteremia (*Escherichia coli*) accompanying three episodes of pyelonephritis. Peritonitis following cecal perforation occurred in one patient who developed colonic pseudo-obstruction. Superficial wound infections[2] and four cases of *Candida difficile* colitis caused the remaining infections. The only infection-related graft loss was from a mycotic pseudoaneurysm of the iliac arterial anastomosis following transmission of candida from an infected allograft. Of 10 viral infections, 8 were caused by cytomegalovirus (CMV) (gastritis, 7; viral syndrome, 1). The others included recurrent genital herpes and reactivation of Epstein-Barr virus (EBV) in a patient who presented with diffuse lymphadenopathy. Not unexpectedly, three seronegative patients receiving allografts from seropositive donors developed symptomatic CMV disease (3 of 9 or 33%). In comparison, no CMV was documented in 20 seronegative recipients receiving seronegative grafts ($P < .01$). The rate of symptomatic CMV in seropositive recipients was 15% or 5 of 34 patients. Patients undergoing secondary transplantation had a similar distribution but higher bacterial and overall rates of infection when compared with primary recipients (0.68 episodes per patient vs 0.27 episodes per patient, $P < .05$, Table 2).

DISCUSSION

Infections remain an important cause of morbidity after kidney transplantation and can be influenced by both technical factors and the need for immunosuppression. Following the introduction of CyA in 1981, we reported a comparison of infections between this "new" agent and the standard azathioprine therapy and found a lower rate of serious infections.[3] Since its introduction in 1989, our enthusiasm for FK 506 only increases as its powerful immunosuppressive ability does not appear to increase the infectious risk. No death in this series was related to infection nor did diabetic patients appear at increased risk.

Our approach to prophylaxis has changed over the last 2 years. All patients receive Bactrim and none have developed *Pneumocystis carinii* pneumonia. Two patients (3%) developed non-CMV viral infections in the FK 506 group and when compared with the early report of 16 patients (25%) this impressive reduction in symptomatic herpes infection may be due to the introduction of acyclovir prophylaxis prior to the FK 506 trial. Donor transmission of candida resulted in the only allograft loss due to infection.

The higher infections seen in the secondary group are likely due to the longer duration of immunosuppression. Interpretation of these observations must be met with caution as changes in management and prophylaxis have occurred since our early report on CyA-treated patients. As well, follow-up has been less than 11 months overall.

The ability to decrease steroid usage, while maintaining adequate single agent immunosuppression, suggests that FK 506 may be a superior drug and this may be an important factor in the relative freedom from serious infections.

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