1271

Infectious Complications of Pediatric Liver Transplantation Under FK 506

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THE introduction of cyclosporine (CyA) has been associated with the evolution of liver transplantation as an effective therapy for children with end-stage liver disease. However, long-term toxicity of CyA and failures due to chronic rejection have prompted evaluation of the new immunosuppressant, FK 506, in pediatric liver transplant recipients at the Children's Hospital of Pittsburgh. The purpose of the following case-control study was to compare the infectious complications seen in patients treated with FK 506 to randomly assigned recent historical controls treated with conventional immunosuppression.

METHODS

Beginning in October 1989, children undergoing first-time orthotopic liver transplantation (OLT) were eligible to participate in a historically controlled, clinical evaluation of the new immunosuppressant, FK 506. A single control was randomly selected from a set of matched candidate controls for each patient treated with FK 506. Matching was performed for age (within 6 months), primary diagnosis, and "UNOS" severity score as soon as possible after the transplant. Inpatient and outpatient charts were systematically reviewed utilizing standardized datasheets and definitions[1] to compare 90-day outcome. Datapoints from the inpatient chart review included patient outcome, immunosuppressive therapy, episodes of rejection, and episodes of infection.

Maintenance immunosuppressive management, as well as the treatment of rejection in the two groups of patients was as previously described.[2,3]

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

RESULTS

Sixty-one children were treated with FK 506 as their primary immunosuppressant between October 1989 and October 1990. Fifty-one controls were identified for these patients. No control was identified for 10 patients because of either an unusual diagnosis or a common diagnosis presenting for transplant at an unusual age. However, for the purpose of this analysis, these unmatched patients were included in the FK 506 group.

Congenital diseases, including biliary atresia and neonatal hepatitis, were the most common diagnoses in both groups. The mean age of the FK 506 group was 4.4 years compared to 3.4 years in control patients (P = NS). This difference in age is accounted for by the 10 unmatched patients who tended to be older (mean = 8.7 years). Six of the 61 patients treated with FK 506 died in the first 90 days posttransplant compared to 13 of 51 control patients (P = .06) Two fo the deaths in control patients occurred during the primary transplant procedure. Six of 61 children treated with FK 506 required retransplantation compared to 10 of 51 control patients (P = NS).

An overview of the infectious complications seen in both treatment groups is shown in Table 1. The mean number of infectious episodes was significantly less in patients treated with FK 506 compared to controls (1.2 vs 1.8, $P < .05$). The type and timing of infection were similar in the two groups.

The mean onset of bacterial infection was 23 days after the transplant, and was not different between the two groups. The most common infection in each group was bacteremia (Table 1), and the most common pathogens were gram-positive organisms. The major difference between the two groups of patients was the frequency of

Table 1. Overview of Infectious Complications During the First 90 Days After Pediatric OLT

	FK 506	Control
No. patients	61	51
Infectious episodes	76	96
Episodes/patient	1.2	1.8*
Fatal infections	2	7†
Bacterial	36	55
Bacteremia	13	32
Line-associated	5	19
Other source identified	4	10
Intra-abdominal (nonbacteremic)	5	8
Enteritis	4	4
Wound	4	2
Pneumonia (nonbacteremic)	3	3
Otitis media/sinusitis	8	4
Urinary tract	2	4
Viral infections	30	33
Cytomegalovirus	12	13
Invasive	9	9
Adenovirus	4	7
Invasive	0	5
EBV/PTLD	1	1
Fungal infections	7	6
Mixed infection‡	3	2

*$P < .05$. †$P = .08$; ‡mixed bacterial and fungal infection.

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catheter-associated bacteremia, and is explained by a change in our usage of central venous catheters. After exclusion of catheter-associated bacteremias, the difference in the mean number of infections is no longer significant.

The overall incidence of viral infection was similar in the two groups (Table 1). The mean onset of viral infection was 33 days after transplantation and was not different in either treatment group. CMV was the most common pathogen, and caused invasive disease in the majority of episodes in both groups. Adenovirus was the next most common pathogen; invasive disease appeared to be more common in controls.

Isolated fungal infections were noted in seven of the children treated with FK 506 compared to six control patients. Mixed infections, consisting of *Candida* species and bacteria, were additionally noted in three FK 506 and two control patients. Infection due to *Aspergillus fumigatus* contributed to the death of one and caused pneumonia in another child with cystic fibrosis transplanted under FK 506. The remaining fungal infections were due to *Candida* species. Despite the fact that five episodes of invasive candidiasis were noted in both treatment groups, the only death due to fungal disease identified during the study period was the previously mentioned child who had concurrent asperillosis of his heart and disseminated candidiasis (Table 2).

Pathogens and clinical syndromes associated with infectious deaths are shown in Table 2. A trend toward an increase in fatal infections was observed in the control group (2 of 61 vs 7 of 51, $P = .08$). Severe pneumonitis, associated with adult respiratory distress syndrome, was the most common fatal infectious syndrome observed in this study.

Table 2. Infectious Deaths After Pediatric OLTx

Immunosuppression	Pathogen	Clinical Syndrome
FK 506	Aspergillus	Carditis
	Candida	Disseminated disease
FK 506	CMV	Pneumonia/ARDS
Control	*S. aureus*	Septic shock
Control	*E. cloacae*	Septic shock
Control	*E. cloacae*	Pneumonia ARDS
Control	Adenovirus	Pneumonia ARDS
Control	Adenovirus	Pneumonia ARDS
	CMV	
Control	CMV	Pneumonia ARDS
Control	Influenza A	Pneumonia/ARDS

DISCUSSION

This study suggests that the type, timing, and frequency of infections seen after liver transplantation are similar in children receiving FK 506 as immunosuppression compared to recent historical controls treated with conventional immunosuppression. The decreased rate of bacterial infections among patients treated with FK 506 is likely explained by a dramatic reduction in our current use of central venous catheters, which preceded the onset of this clinical trial.

A trend toward an increase in fatal infections was observed in the control group in this study suggesting that patients transplanted under FK 506 may experience less infection-associated mortality than those treated with traditional immunosuppressive regimens. Although limited by the small number of patients observed in this study, the trend appeared to hold for both bacterial and viral infections. This observation may be explained by a decreased use of corticosteroids and OKT3 in the children treated with FK 506.[4]

Evaluation of the first 3 months after pediatric liver transplant demonstrates no increase, and perhaps, a decrease in infectious disease morbidity and mortality in pediatric liver transplant recipients treated with FK 506. These findings, along with a trend toward increased survival and the previously reported benefits of less steroid and antihypertensive requirement in these children, suggests that FK 506 is superior to conventional immunosuppression. Continued follow-up for late infectious sequelae, including the development of posttransplant lymphoproliferative disease, are necessary to complete these observations.

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