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Infections With FK 506 Immunosuppression: Preliminary Results With Primary Therapy

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INFECTIOUS complications following orthotopic liver transplantation (OLT) remain the major cause of patient mortality and morbidity. Despite advances in technical and preservation management, these complications have not decreased significantly with present immunosuppression regimens. We have initiated the first human clinical trials of OLT under FK 506 immunosuppression, and report the infectious disease profile in this early experience.

METHODS

Only those patients undergoing primary OLT were enrolled in this pilot study and followed prospectively from the time of surgery to death or discharge. A comparable group of recent control patients receiving CyA and undergoing primary OLT were computer-matched for age, diagnosis, and United Network for Organ Sharing criteria and are included for comparison. Due to the limited follow-up in the FK 506 group, a similar postoperative time interval was identified for the controls, allowing comparison of infections occurring during the same time interval.

Immunosuppression

The study patients received an intravenous induction dose of FK 506 at 0.15 mg/kg and 1 g methylprednisolone at the time of surgery. Intravenous maintenance doses of FK 506 at 0.075 mg/kg twice a day were given until the patients were able to take an oral preparation of 0.15 mg/kg in two divided daily doses. A rapid daily taper from 1 g to 20 mg of methylprednisolone was given over the subsequent 5 days.

The control patients received an intravenous induction dose of CyA at 3 mg/kg, which was maintained until an oral diet was resumed; the subsequent dosage was then regulated by daily serum monitoring to maintain therapeutic CyA levels. A rapid daily methylprednisolone taper from 1 g to 20 mg d was also used. Rejection episodes were treated with 1 g steroid pulses or recycles with conversion to OKT3 for persistent acute cellular rejection.

Definition of Infections

We have previously reported and classified infections as severe and nonsevere, as shown in Table 1.[1] Briefly, bacteremia were defined by the isolation of staphylococcus, *Candida* sp, or aerobic gram-negative rods in at least one blood culture. Other pathogens required isolation of bacteria in two blood cultures or in one positive blood culture, and in a culture from a known site of infection. Wound infections required heavy growth of a pathogen in the presence of erythema and purulent drainage at the incision. Peritonitis required growth of a pathogen from ascitic fluid and a neutrophil count of >300 polymorphonuclear cells. Cholangitis required isolation and heavy growth of a pathogen from bile, the presence of fever, and elevated liver function tests. Pneumonia required the new appearance of lung infiltrates on chest x-ray, onset of new respiratory symptoms and/or hypoxemia, and the isolation of pathogens from sputum. *Clostridium difficile* colitis required a new onset of diarrhea and the presence of *C difficile* toxin in stool.

Symptomatic cytomegalovirus (CMV) was defined as a febrile syndrome associated with viremia and/or the presence of virus in tissues (liver, lung, or gastrointestinal tract), confirmed by histology. Candidiasis required a positive fungal blood culture and/or growth of *Candida* sp from a sterile site.

Prophylaxis

All patients received perioperative antibiotics consisting of ampicillin and cefotaxime at 4 g/d for 72 hours. Oral acyclovir, 200 mg twice daily, trimethoprim-sulfamethoxazole, 80 mg/TMP/400 SMZ daily, and mycostatin, 500,000 U 4 times a day, were given to all patients.

Statistics

All proportions were analyzed by χ^2.

RESULTS

The characteristics of the patient population are shown in Table 2. The two groups are comparable in terms of demographics and follow-up. Of note is that no death in the FK 506 group was related to infection, while both deaths in the control group were. A significantly higher incidence of overall infections was seen in the control group, as shown in Table 3 ($P = 0.05$). Although no significant differences were noted when bacterial or fungal infections were compared, there was a striking difference ($P = 0.02$) in those patients who developed symptomatic CMV infection.

The only infections seen in the FK 506 group were bacterial and included two abdominal wound infections (*Enterobacter cloacae* [one], *Staphylococcus aureus* [one]) requiring simple drainage and antibiotics, cholangitis (*Streptococcus faecium*) due to an obstructing biliary

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Table 1. Definition of Infections

Severe	Nonsevere
Bacteremia, fungemia	Bacterial sinusitis
Invasive fungal infection	Cystitis
Wound infection	Localized herpes zoster
Intraabdominal abscess	Localized herpes simplex
Peritonitis	
Symptomatic CMV	
Clostridium difficile colitis	
Herpes simplex tissue	
Pneumonia	

stent found at exploratory laparotomy in the early postoperative period, and peritonitis (*S aureus*) not requiring operative intervention. Thirteen infections were noted in 11 control patients and included peritonitis (two), pneumonia (two), candidiasis (two), *C difficile* colitis (two), and symptomatic CMV (five).

No patient in the FK 506 group acquired a symptomatic CMV infection, compared with five in the control group. Nonsymptomatic CMV or simple viral shedding was seen in three FK 506 patients. Recovery of CMV in the urine of two seropositive patients suggested reactivation, while a positive blood buffy coat in one seronegative patient receiving a seropositive graft suggested the occurrence of a primary asymptomatic infection. All five symptomatic patients in the control group had received intense immunosuppression with increased steroid pulse and azathioprine therapy; three were also given OKT3 for persistent rejection. Four seronegative patients in the FK 506 group received grafts from seropositive donors and none developed a symptomatic infection, while five of seven similar control patients became symptomatic (CMV hepatitis [four], CMV gastritis [one]). Three deaths were documented. The sole FK 506 death was a 55-year-old woman with primary biliary cirrhosis and asymptomatic primary pulmonary hypertension due to a sudden hemodynamic decompensation and myocardial infarction on the 14th postoperative day. The two control deaths occurred outside the follow-up time period and were due to pneumonia at 61 days in one patient and to progressive multifocal leukoencephalopathy at 248 days in the other.

Table 2. Comparative Demographics of 20 Primary Liver Transplant Recipients of FK 506 and Their CyA-Treated Controls Followed for Less Than 62 Days

	FK 506 (n = 20)	Control (n = 20)
Male/female ratio	12/8	12/8
Mean age (yr)	40.5	39.0
Range (yr)	18-64	20-60
Mean follow-up (d)	35.5	36.3
Range (d)	14-62	24-62

Table 3. Frequency of Severe Infections in Two Matched Groups of Liver Recipients

	FK 506 (n = 20)	Control (n = 20)
Total patients		
Patients infected	4	11 $P < .05$
Infection		
Bacterial	4	4 NS
Fungal	0	0 NS
Viral	0	5 $P < 0.02$
Infection-related death	0	0 (2)*

* Two deaths, pneumonia at 61 days and progressive multifocal leukoencephalopathy at 248 days.

DISCUSSION

Infections following liver transplantation remain the most serious complication during the postoperative period. In a previous study from our institution, 67% of 101 consecutive patients undergoing primary OLT developed severe infections, with symptomatic CMV infections noted in 22 patients (22%) and associated with five deaths.[1]

This pilot study of patients receiving FK 506 is encouraging in that the seemingly powerful immunosuppressant ability of the drug is not overshadowed by an increase in infectious complications. In fact, when compared with a similar control group receiving standard therapy and followed during the same early postoperative time interval, there was a significantly lower incidence of overall infections. The FK 506 infections were bacterial and can also be seen in a nonimmunosuppressed population. The lack of a statistical difference between the bacterial and fungal groups suggests that viral infections made the difference.

The most striking finding was the incidence of symptomatic CMV infection. It is well-known that such infections occur following increased immunosuppression, which is common to rejection therapy. The FK 506 patients had significantly fewer rejection episodes and thus received less immunosuppression overall. No FK 506 patient was given OKT3, which may prove to be the most important omission in the antirejection protocol, as its role in dissemination of CMV infection has been reported.[2,3] Also, rejection in itself has been shown to enhance CMV infection in a murine model.[4] The simultaneous occurrence of CMV in patients with other severe bacterial and fungal infections has led some investigators to suggest that its mere occurrence is immunosuppressive.[5] We can only speculate that the elimination of CMV infections may decrease these other serious infections. We caution against firm conclusions regarding late infections, as the maximum length of follow-up in these patients is limited to 62 days. However, the diagnosis of CMV infection in the control patients was at a mean of 31.5 days, which was less than the 35-day mean follow-up of the four seronegative FK 506 patients. Our data suggest that the use of FK 506 in the early posttransplant period is associated with modest infectious complications, low mortality, and no observed

symptomatic CMV. Longer follow-up and careful evaluation of these patients will be necessary.

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