1524

Infections During a Randomized Trial Comparing Cyclosporine to FK 506 Immunosuppression in Liver Transplantation

S. Kusne, J. Fung, M. Alessiani, M. Martin, J. Torre-Cisneros, W. Irish, L. Ondick, A. Jain, K. Abu-Elmagd, S. Takaya, S. Todo, and T.E. Starzl

WE PREVIOUSLY reported our experience of infectious complications occurring following liver transplantation (OLT) under an experimental immunosuppressive agent FK 506.[1] In February 1990 we initiated a randomized trial comparing this new drug to cyclosporine (CyA) in patients undergoing their first OLT. In this report we analyzed the infectious complications in the first 110 patients enrolled in this study.

METHODS

Patient Population

Characteristics of the patient population is shown in Table 1. The patients enrolled in this study were considered relatively low-risk candidates who did not have significant kidney, heart, or lung disease, were not human immunodeficiency virus (HIV) or B hepatitis carriers, and in whom the transplant operation was thought to be functionally adequate. There were a total of 110 patients enrolled in this study between February and December 1990, 53 on CyA and 57 on FK 506. The median follow-up was 341 days. All patients were followed prospectively for infections. Most patients had surveillance viral cultures at 2-week intervals for the first 2 months and monthly during the following 4 months. Other cultures were done when clinically indicated.

Immunosuppression

Patients on CyA were given an IV dose of 4 mg/kg/d and when able to take oral medications, 8 mg/kg was administered in two divided doses. Patients on FK 506 were given a continuous IV infusion at 0.1 mg/kg/d and later changed to PO at 0.15 mg/kg every 12 hours. Steroid induction included 1 g of methylprednisolone and steroid maintenance 20 mg prednisone. Treatment of acute rejection included methylprednisolone "bolus" and/or steroid "recycle." Steroid-resistant rejection was treated with OKT3 monoclonal antibody (MAb), or conversion to FK 506 for those patients on CyA.[2]

Prophylaxis and Infection Definitions

We used our previous definitions of infection[3] and subdivided them in major categories (bacterial, viral, fungal, protozoal). Infections not included in the analysis were: bacterial sinusitis, cystitis, line infection without bacteremia, and localized herpes infection. Antimicrobial prophylaxis included 3 g/d cefotaxime or ceftizoxime IV together with 4 g/d ampicillin for 72 hours, 2 million U/d PO nystatin, trimethoprim/sulfamethoxazole 80 mg/400 mg PO every day, and acyclovir between 400 mg and 3200 mg PO for the duration of 6 months.

Table 1. Characteristics of the Patient Population

	CyA	FK 506
No. Patients	53	57
Male/female ratio	33/20	31/26
Mean age ± SD (y)	43.5 ± 10.2	42 ± 11.4
Median follow-up (d)	342	341
Range follow-up	19-492	93-497
Patients >1 y follow-up	22	23
One-year survival (%)	84	95

Statistics

There were 37 patients who were initially treated with CyA but were later continued on FK 506. These patients posed a problem for statistical analysis. It was felt that treating these patients as withdrawals or creating a third arm would bias the results of the study. Therefore, in order not to undermine the reasons for randomization, the statistical analysis was performed by intention to treat. Survival rates and infection-free rates were calculated by the Kaplan-Meier method. Proportions were analyzed by using the chi-square test of association. A P value $< .05$ was considered statistically significant.

RESULTS

The 110 patients enrolled in the study were prospectively followed for infectious complications. Twenty-two and 23 patients treated with CyA and FK 506, respectively, were followed for more than 1 year. The population in the two groups was similar for liver diagnosis, age, and male/female ratio (Table 1).

Of the 53 patients initially treated with CyA, 37 failed the prescribed regimen for CyA and were converted to FK 506.[2] The median time to the conversion was 10 days. Sixteen patients currently remain on CyA. For purpose of this study, we will refer to "CyA" as all patients who were initially randomized to receive CyA.

One year survival was 84% for CyA and 95% for the FK 506 group. The 1-year infection-free rate was 46% for CyA and 61% for FK 506 group (P = .32). The frequency of various infection categories is shown in Table 2. Infections were also expressed as the number of episodes of infection per infected patient. Overall 50.9% of the CyA group and 38.6% of the FK 506 group had at least one infection

From the Departments of Surgery, Medicine and Infectious Disease, University of Pittsburgh, Pennsylvania.

Supported by research grants from the Veterans Administration and project grant no. DK 29961 from the National Institutes of Health, Bethesda, Maryland.

Address reprint requests to Dr Kusne, 3601 Fifth Ave, 5C Falk, Pittsburgh, PA, 15213.

0041-1345/92/$3.00/+0

Table 2. Percentage of Infected Patients and Number of Episodes per Infected Patients Subdivided in Categories of Infection

	Percent Patients Infected		Episodes/Infected Patients	
	CyA	FK 506	CyA	FK 506
Bacterial	43.4	28.1	1.7	1.4
Viral	24.5	19.3	1.4	1.0
Fungal	3.8	3.5	1.0	1.5
Protozoal	3.8	0	1.0	0
Total	50.9	38.6	2.2	1.6

episode with 2.2 and 1.6 episodes per infected patients, respectively. There was a trend toward a lower frequency of bacterial infections in the FK 506 group ($P = .14$). When bacteremias were analyzed separately, they were seen more frequently in the CyA group (26.4% vs 7.0%, $P = .013$). The most frequent pathogens isolated from blood were aerobic gram-positive cocci, especially *Staphylococcus aureus* and enterococci. *Enterobacter cloacae* was the most frequent aerobic gram-negative isolate. Table 3 lists the overall infection episodes observed in the two groups. The most frequent infection was cytomegalovirus (CMV) followed by *Clostridium difficile* colitis, wound infection, and bacterial pneumonia. There were a total of 15 episodes of symptomatic CMV in the CyA and 10 episodes in the FK 506 group with a frequency of 20.8% and 17.5%, respectively. The CMV experience in this trial is summarized separately.[4]

Other factors that played a role in the development of infections were examined. There were eight patients in the CyA group and four patients in FK 506 group who had more than one transplant operation. The infection rate in both groups was higher compared with patients with only one transplant operation. The use of OKT3 in the CyA group was 32.1% compared with 17.5% in the FK 506 group ($P = .12$). The infection rate was higher after OKT3 in both groups. The use of additional steroids in form of "bolus" or "recycle" was higher in the CyA group (75.5% vs 52.6%, $P = .02$).

Table 3. Number of Infection Episodes and Number of Patients Infected in the Two Groups

	No. Patients		No. Episodes	
Type Infection	CyA	FK 506	CyA	FK 506
Pneumonia	3	3	3	5
Wound infection	5	2	7	2
Peritonitis	3	3	3	3
C. difficile colitis	5	6	5	6
Cholangitis	3	4	3	4
Bacteremia	5	1	6	1
Abdominal abscess	2	0	2	0
Others	8	1	9	1
Symptomatic CMV	11	10	15	10
Symptomatic EBV	3	1	3	1
Invasive candidiasis	2	2	2	2
Histoplasmosis	0	1	0	1
P. carinii pneumonia	2	0	2	0

DISCUSSION

We previously reported lower infection rates with the use of the new immunosuppressive drug FK 506 compared with historical controls.[5] In the current study we were able to compare infectious complications in a randomized trial using CyA and FK 506. Because 70% of the patients in the CyA arm were later placed on FK 506, the comparison in infection rates is between FK 506 patients on one side and CyA or "initially CyA" patients on the other.

Although the types of infection were similar in the two groups, the frequency of bacterial infection was lower in the FK 506 group especially when bacteremias were analyzed separately. The reduced requirement for steroids and OKT3 in the FK 506 group may explain the lower frequency of bacterial infections observed in this group. Most infection episodes occurred in patients who were initially placed on CyA and later converted to FK 506. This group had many risk factors for development of infectious complications. Twenty-two percent of these patients underwent retransplantation, 78% received additional steroids, and 38% received OKT3 (vs 7%, 55%, and 17% in the FK 506 group, respectively). In the group randomized to FK 506, we were able to use reduced amount of immunosuppressive agents to control rejection and the rate of retransplantation was lower. These factors are known to increase the risk of infection in liver transplantation.

Symptomatic CMV infection was still the most frequent infection in both groups, however it was not associated with death in either group. Although the number of symptomatic Epstein-Barr virus (EBV) infections were equivalent in both groups, one death associated with posttransplantation lymphoproliferative disease (PTLD) was seen in the CyA group. Invasive fungal infections were associated with high mortality rate in both groups with two deaths in each. Two patients developed *Pneumocystis carinii* pneumonia and both were not taking prophylactic drugs.

In summary, the use of FK 506 has not resulted in an increase in the infection rate, and by eliminating the need for augmented immunosuppression may actually result in a lower incidence of infections.

REFERENCES

1. Alessiani M, Kusne S, Martin M, et al: Transplant Proc 23:1501, 1991

2. Fung J, Abu-Elmagd K, Jain A, et al: Transplant Proc 23:2981, 1991

3. Kusne S, Dummer JS, Singh N, et al: Medicine 67:132, 1988

4. Alessiani M, Kusne S, Fung J, et al: Transplant Proc 23:3040, 1991

5. Alessiani M, Kusne S, Martin M, et al: Transplant Proc 22:44, 1990