COMPLICATIONS IN LIVER TRANSPLANTATION

CMV Infection in Liver Transplantation Under Cyclosporine or FK 506 Immunosuppression

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THE herpesvirus family is a frequent cause of infectious complications after liver transplantation.[1,2] In particular, cytomegalovirus (CMV) infection has been identified in our historical series as the most frequent infection seen either under cyclosporine (CyA)- or FK 506-based immunosuppression.[3,4]

A direct comparison between these two immunosuppressive regimens has been addressed as part of a randomized trial, allowing us to determine whether there are any differences in terms of the incidence and characteristics of CMV infection in patients immunosuppressed with either FK 506 or CyA.

MATERIALS AND METHODS

The characteristics of the study population, the immunosuppressive protocol, and the viral prophylaxis utilized are summarized in Table 1.

Briefly, a total of 110 adults underwent orthotopic liver transplantation and were enrolled in this trial. The age, gender, duration of follow-up time, original liver disease, antimicrobial prophylaxis regimens utilized, and the frequency of various donor/recipient CMV serologic matches were comparable in the two groups. The minimum duration of follow-up time was 6 months. CyA and FK 506 were administered initially as a constant infusion at the dosage shown in Table 1. Conversion to the oral route was accomplished as soon as it was feasible. Both groups received baseline steroid treatment and similar therapy for rejection (when necessary) consisting of augmented steroids and/or OKT3. The patients treated with CyA with uncontrolled rejection were switched to FK 506.

Table 1. Patient Population Under Study

	CyA	FK 506
Patient population		
No. patients	53	57
Sex (M/F)	33/20	31/26
Mean age (y)	43.5	42.0
Mean follow-up (d)	342	341
One-year survival (%)	86	96
Immunosuppressive protocol		
IV continuous infusion (mg/kg per day)	4	0.1
PO dose every 12 hours (mg/kg)	8	0.15
Viral prophylaxis		
Oral acyclovir from 400 to 3200 mg for 6 months in both groups		

Only symptomatic CMV infections were considered for this study. Primary infection was defined by isolation of CMV from clinical specimens with seroconversion. Viral syndrome was defined as isolation of CMV in a patient with temperature elevation >38°C for at least 1 week, without any other identifiable agent being recognized as a potential cause for the syndrome. Localized CMV disease was defined as tissue invasion of a single organ determined either histopathologically or by culture of the virus from the tissue. Disseminated CMV disease was defined as tissue involvement of two or more noncontiguous sites.

Routine viral surveillance was accomplished by scheduled cultures and serologic determinations at 2-week intervals for the first 2 months, and then once a month for the duration of the follow-up. Additional clinical evaluations were obtained when symptomatic disease was suspected.

Statistical analysis was based on the intention to treat. Proportions were analyzed using the chi-square test of association.

RESULTS

Of the 110 patients enrolled in this study, 10 died during the follow-up period. None of the deaths occurring in either group were a result of a CMV infection. The 1-year survival rate was 86% for the CyA group and 96% for the FK 506 group.

Symptomatic CMV infection was diagnosed in 21 patients. In the CyA group, 11 of 53 patients (20.8%) developed a total number of 15 episodes of symptomatic CMV infection. The number of episodes per infected patient in this group was 1.4. In the FK 506 group, 10 of 57 patients (17.5%) developed a total of 10 different CMV infections. In this group, the number of episodes per patients was one.

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Table 2. Rate and Site of Infection in CyA- and FK 506–Treated Patients

	CyA (n = 53)	FK 506 (n = 57)
Results		
% Patients infected	20.8	17.5
Total episodes	15	10
Episode/infected patient	1.4	1
Site of occurrence		
Syndrome	2	1
Gastritis	4	3
Hepatitis	4	3
Retinitis	1	0
Multiple organs	3	3
Vasculitis	1	0

The sites of occurrence for each single episode are summarized in the Table 2. As shown in this table, the most frequent site of infection were the liver and the GI tract. Multiple organs were involved in each group on three occasions.

Analysis of the donor and recipient CMV serology demonstrated in both CyA and FK 506 groups that both the seronegative and the seropositive recipients had a greater risk of symptomatic CMV disease if their donor was seropositive. Of the 63 seropositive recipients, 33 received a liver from a seronegative donor. Only 1 of these recipients (3%) developed a clinical CMV infection compared to 8 (26.7%) of the 30 patients that received an organ from a seropositive donor. The remaining 47 recipients were seronegative. In 25 of these, the donor was also seronegative. Only 2 (8%) had symptomatic CMV. For the other 22 patients, the donor was seropositive. The incidence of CMV infection in this group was dramatically increased, with 10 patients (45.5%) experiencing a clinical CMV infection.

The influence of retransplantation and the use of OKT3 were evaluated also. Retransplantation was performed in 8 patients under CyA and 4 patients under FK 506 treatment. In the CyA group, CMV infection was diagnosed in 9 of the 45 patients that received one transplant (20%) and in 2 of the 8 who were retransplanted (25%). In the FK 506 group, a single transplant was associated with a frequency of CMV infection of 13.2% (7 of 53 patients), while the rate of CMV infection in the retransplant cases increased to 75% (3 of 4 patients). In this last group, the difference was statistically significant (P = .0142) (Fig 1).

OKT3 was used in 17 patients receiving CyA, 5 of whom developed a clinical CMV infection (29.4%). In the FK group, 10 patients received OKT3 and 3 experienced a CMV infection (30%). For both groups, the rate of CMV in patients not receiving OKT3 was reduced by 50% as compared to those who did (Fig 2).

Of particular interest was the finding that within the CyA group, CMV infection was associated with other types of infection in 9 patients (82%, 11 infected cases total). In the FK 506 group, this happened in only 5 of 10 cases (50%) (NS).

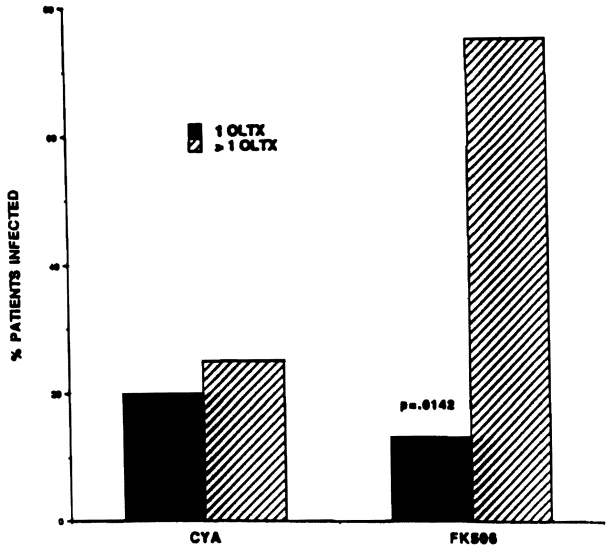

Fig 1. The rate of CMV infection increased dramatically after retransplantation in the FK 506 group. In the CyA group, the difference is minimal.

Thirty-seven patients in the CyA group were switched to FK 506 for persistent rejection. Nine of these had a CMV infection (82% of the patients infected in the overall CyA group). The CMV infection occurred either just before or immediately after the switch in 5 of the 9 patients. Only 1 patient in the FK 506 group was converted to CyA. In this case, a multiple-organ CMV infection was evident while the patient was still on FK 506. As expected, most of these "switch-over" patients experienced a very complicated postoperative course, with several episodes of rejection, liver failure, retransplantation, having a requirement of

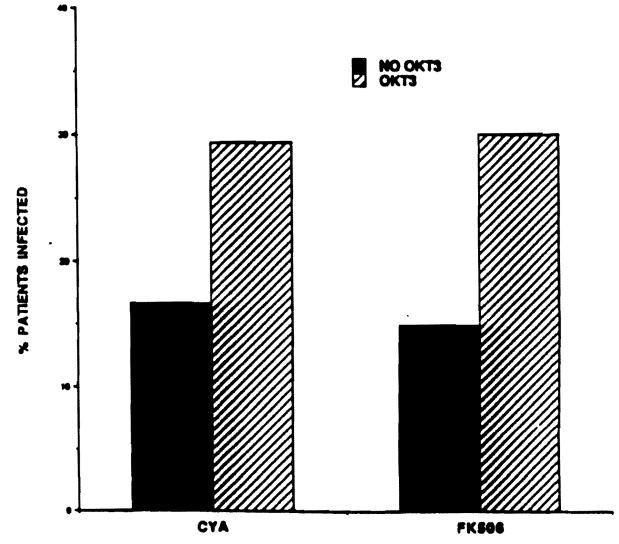

Fig 2. The use of OKT3 increased the incidence of symptomatic CMV infection by 50% in both CyA and FK 506 groups.

high doses of steroids, and the use of OKT3 before the conversion.

DISCUSSION

CMV infection is one of the more frequent causes of morbidity in immunocompromised patients, particularly those having received either a solid organ or bone marrow transplant.[5–7] Our previous experience with liver transplantation confirms this statement. In a population of 101 liver transplant recipients immunosuppressed with CyA and steroids, 22% developed a symptomatic CMV infection.[3] At that time, no specific immunoprophylaxis or therapy for CMV infection was available.

More recently, a similar population of 110 patients, treated with FK 506 and low-dose steroids, was studied.[4] In this group, high doses of acyclovir were used for viral prophylaxis, and DHPG (gancyclovir) was available as a therapeutic agent for CMV infection. In spite of these differences between the two series, the frequency of CMV infection remained the same (21%). Nevertheless, an important difference was noted: infections were no longer life threatening to the same degree as before. In the initial series, CMV caused the death of five patients while in the later series, none of the patients died as a result of a CMV infection.

In the current randomized study, the frequency of CMV infection (19%) and its severity (no deaths due to CMV) are quite comparable to those obtained in our initial series.[4] No statistical difference was seen between the CyA and the FK 506 group in terms of the frequency of CMV infection and the site of occurrence. However, the FK 506 population experienced a lower number of episodes of symptomatic CMV (10 vs 15) than did the CyA group.

In this randomized trial, a high incidence of patients were converted from CyA to FK 506. This may confuse the interpretation of the results, since some of them developed their CMV infection after the switch. Review of the immunosuppressive course of the patients revealed that patients who developed symptomatic CMV infection after conversion from CyA to FK 506 were considered overimmunosuppressed. It is unlikely that FK 506 alone was responsible for the CMV infection in these patients. Fig 3 shows the difference between the two groups in terms of their requirement for additional immunosuppression. The higher incidence of bacterial and fungal infections in patients who received augmented immunosuppression suggests that these patients are at higher risk for all infections. If the baseline immunosuppressive regimen is able to reduce the requirement of the augmented immunosuppression, a reduced frequency of CMV infection might be anticipated. However, this hypothesis was not entirely verified in the randomized study. It appears that other factors, such as donor and recipient serology, play an important role.

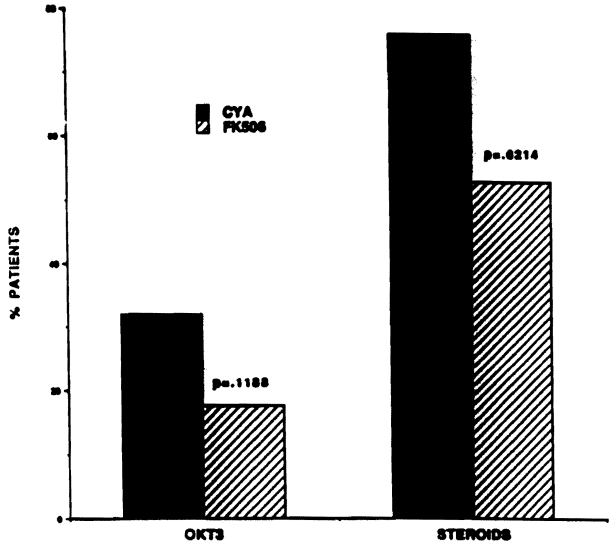

Fig 3. The requirement for additional immunosuppression was higher in the CyA group. This overimmunosuppression was necessary to control the rejection.

REFERENCES

1. Singh N, Dummer JS, Kusne S, et al: J Infect Dis 158:124, 1988

2. Paya CV, Hermans PE, Washington JA, et al: Mayo Clin Proc 64:555, 1989

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

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

5. Dunn DL, Simmons RL: Infect Surg 8:164, 1989

6. Dummer JS, Hardy A, Poorsattar A, et al: Transplantation 36:259, 1983

7. Stratta RJ, Shaefer MS, Markin RS, et al: Arch Surg 124:1443, 1989