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CYTOMEGALOVIRUS INFECTION OF THE UPPER GASTROINTESTINAL TRACT FOLLOWING LIVER TRANSPLANTATION—INCIDENCE, LOCATION, AND SEVERITY IN CYCLOSPORINE- AND FK506-TREATED PATIENTS[1,2]

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One hundred and forty randomly selected liver transplant recipients were studied before and after primary orthotopic liver transplantation for the presence or absence of CMV enteritis. Following OLTx, 65 patients were treated with cyclosporine A and 75 were treated with FK506. The two groups were similar with regard to the incidence, location, and outcome of their upper gastrointestinal CMV infection. Prior to OLTx, only one patient had evidence of enteric CMV infection. The incidence of CMV enteritis post-OLTx was 27.7% in the CsA-treated group and 20% in the FK-treated group. During the first posttransplant month, no patient in the FK-treated group developed CMV enteritis, compared with 11.5% of the patients who were treated with CsA ($P<0.05$). Gastric CMV was found in over 80% of those positive for any organ in either group. In addition to CMV infection of the upper gastrointestinal tract, clinically evident CMV disease involved more nonenteric organs in the CsA-treated group than in the FK-treated group. In the CsA-treated group, CMV-negative patients had a statistically higher 1-year survival rate (100%) than CMV-positive patients (77.8%) ($P<0.05$). In the FK-treated group, no difference in survival was observed between CMV-positive or CMV-negative cases at 1 year. Of the patients on CsA, 20% received OKT3 for persistent rejection, as compared with 13% in the FK-treated group. The patients receiving both CsA and OKT3 had a higher rate of upper gastrointestinal CMV infection than did FK-treated patients who also received OKT3 therapy (38.5% versus 20%, respectively). Based upon these data, it can be concluded that (1) patients receiving FK have a lower incidence of enteric CMV infection; (2) following OLTx, upper gastrointestinal CMV infection presents later in FK-treated patients; (3) the stomach is the most frequently involved organ in the UGIT; (4) FK-treated liver recipients have less severe enteric CMV infection than do CsA-treated patients; (5) enteric CMV is not a major cause of mortality in liver transplant recipients; and (6) in patients receiving FK, those who require OKT3 therapy do not appear to be at a greater risk for the development of CMV enteritis than those who do not.

Gastrointestinal cytomegalovirus infection is a major clinical problem for organ transplant recipients because of its prevalence (*1*), morbidity, and potential lethality (*2–4*). Earlier studies from Pittsburgh have shown that upper gastrointestinal CMV infection is a frequent clinical problem in liver transplant recipients receiving cyclosporine A (*5*). FK506, a potent new immunosuppressive agent, is currently being used in recipients of liver transplants because of its greater potency (*6, 7*) and reduced frequency of untoward side effects (*8*).

The purpose of this study was to compare the incidence, timing, location, and outcome associated with CMV infection of the upper gastrointestinal tract occurring in liver transplant recipients receiving either CsA or FK506.

MATERIALS AND METHODS

Patient population. The study population consisted of 140 patients who underwent primary orthotopic liver transplantation at the University of Pittsburgh between June 1987 and September 1990. Each subject was studied prospectively both before and after transplantation, based solely on the availability of one of the investigators at the time of his or her pre-OLTx endoscopic procedure. The subjects were divided into two groups based on the primary immunosuppressive agent used in each case: group 1 consisted of patients who were given CsA (n=65), while group 2 consisted of patients receiving FK506 (n=75). Patients were followed until they were discharged from hospital, were switched to a new immunosuppressive agent (usually CsA to FK), or were retransplanted for graft failure regardless of the reason. The study population consisted of 70 males and 70 females. Their ages ranged from 16 to 67.5 years, with the mean being 44.3±2.5 years.

Immunosuppressive therapy. Group 1 (CsA treatment): Patients in this group were given an intravenous induction dose for CsA (2 mg/kg) and maintained on a dose of 2 mg/kg intravenously every 12 hr until oral therapy was possible, at which time the dose of CsA was changed to 8 mg/kg orally every 12 hr. All subsequent oral doses were regulated by monitoring daily serum CsA levels to maintain a therapeutic CsA level between 200 and 1000 ng/ml. Patients in this group were also given an initial intravenous dose of methylprednisolone (1 g/day) and maintained at a dose of 20 mg/day intravenously until oral therapy was possible. At this time, a maintenance dose of 20 mg/day of oral prednisone was started. Azathioprine at a dose of 1–2 mg/kg orally was added to the immunosuppressive regimen of those patients who received one or more courses of OKT3 or required a reduction of CsA therapy because of nephrotoxicity.

Group 2 (FK treatment): Patients in this group were given an intravenous induction dose of FK506 at 0.957 mg/kg. Subsequently, FK at a dose of 9.975 mg/kg was given twice a day intravenously until the patient was able to take the medicine orally at a dose of 0.15 mg/kg/day in divided daily doses given every 12 hr. Therapeutic levels of FK506 were maintained between 0.5 and 2.0 mg/ml by adjusting the oral dose as necessary. Patients in this group did not receive methyl-

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prednisolone intravenously but were given a maintenance oral dose of prednisone (20 mg/day) when oral therapy was possible. This dose was reduced on a regular basis as long as no evidence for liver rejection was evident.

Supplemental immunotherapy. Biopsy-proven rejection episodes were treated either with one-gram methylprednisolone "pulses" given intravenously or with a "recycle" of oral prednisone in which the daily dose of prednisone was raised to 200 mg/day and tapered to a maintenance level of 20 mg/day over the subsequent 5 days. Persistent rejection episodes were treated with a 5-day course of intravenous OKT3 at a dose of 10 mg/day.

Endoscopic procedures. All patients underwent scheduled pre-OLTx upper gastrointestinal endoscopy with biopsy of the second portion of the duodenum, gastric antrum, and lower esophagus using an Olympus GIF 2T10 endoscope and large biopsy forceps (Olympus FB 13K). Following OLTx, any symptoms suggesting upper gastrointestinal dysfunction such as nausea, vomiting, gastric stasis, or bleeding was investigated by endoscopy. Many patients were endoscoped on multiple occasions, but always as indicated clinically.

Histologic and virologic methods. Specimens were fixed in 10% formalin, dehydrated, embedded in paraffin, sectioned at five microns, and stained for histological examination with hematoxylin and eosin. All tissues suspicious for CMV infection based on the histology and/or viral culture results were examined further by using immunohistochemical methods for the detection of CMV early and late antigens (*9*).

Tissues for viral cultures were homogenized and cultured for CMV on human foreskin fibroblasts (Bartels Immunodiagnostic Supplies, Bellevue, WA) and A549 human lung carcinoma cell line (M.A. Bioproducts, Walersville, MD). Viral cultures were observed twice weekly for 3 weeks. Early antigen detection in cultures was achieved using MRC-5 cells seeded onto shell vials with centrifugation enhancement and staining with monoclonal antibody to CMV early nuclear antigen (Organon-Technica) at 18–24 hr after plating (*10*).

Blood, urine, and throat cultures were not obtained on these patients unless clinically indicated.

Diagnostic criteria. The diagnosis of CMV enteritis was based on the presence of either of the following criteria: (1) a positive culture of biopsied tissue, or (2) characteristic CMV inclusion bodies in stained tissues with immunohistochemical confirmation.

Statistical analysis. All data are presented as the mean and the standard error of the mean. Chi-square analysis was used to evaluate associations as well as differences between proportions. Differences in the means were tested using the Student's test. A P value of <0.05 was considered to be significant.

RESULTS

The two groups were comparable in terms of age and gender, with almost an equal percentage of males and females in each group. There were no differences between the two groups in the type of liver disease necessitating transplantation (Table 1).

Incidence and timing of CMV infection. Pre-OLTx: Prior to transplantation, CMV infection in the upper gastrointestinal tract was documented in only one patient. Post-OLTx, this patient was randomized to receive CsA (group 1) and was found to have clinically symptomatic CMV infection in the first posttransplant month.

Post-OLTx: The incidence of CMV infection following OLTx was significantly greater than that occurring prior to OLTx in both groups ($P<0.001$). The overall incidence of CMV infection among these liver recipients was 23.6% (33 of 140). A greater incidence of CMV infection was found in the CsA-treated group than in the FK-treated group (27.7% versus 20%, respectively), although this difference in incidence was not statistically significant. The cumulative occurrence of upper gastrointestinal CMV infection in both groups is shown graphically in Figure 1.

TABLE 1. Demographic variables of study population

Variables	CsA group	FK group
Age (years)		
Mean ± SE	42.1±1.7	47±1.6
Range	18–67	16–67.5
Sex		
Male	33	37
Female	32	38
Diagnostic category		
Parenchymatous		
Chronic active hepatitis	20	22
Cryptogenic cirrhosis	9	11
Drug-induced cirrhosis	1	2
Alcoholic cirrhosis	11	17
Hepatoma	2	4
Metabolic liver disease		
Hemochromatosis	0	2
Wilson's disease	1	0
A-1-A deficiency	0	2
Cholestatic disease		
Primary biliary cirrhosis	12	5
Secondary biliary cirrhosis	0	1
Sclerosing cholangitis	2	7
Biliary atresia	1	0
Other		
Fulminant hepatic failure	3	1
Fulminant hepatitis A	1	0
Fulminant hepatitis B	1	0
Budd-Chiari syndrome	1	1
Total (n = 140)	65	75

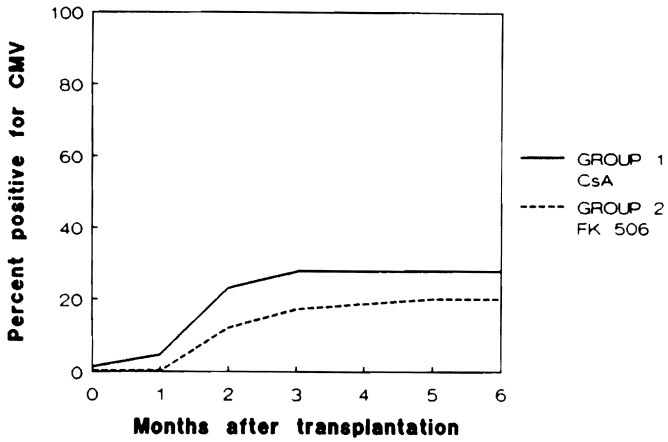

FIGURE 1. Cumulative rate of upper gastrointestinal CMV infection post-OLTx in patients treated with CsA (group 1) or FK506 (group 2).

The mean time interval from the time of transplantation to the date of diagnosis of a CMV infection of the upper gastrointestinal tract was 6.1±0.6 weeks (range, 2 to 11 weeks) in the CsA-treated patients and 8.7±1 weeks (range, 5.1 to 21.7 weeks) in the FK-treated patients ($P<0.05$). As may be seen in Table 2 and Figure 2, no patient in the FK-treated group developed enteric CMV infection in the first postoperative month, compared with 11.5% of patients who were endoscoped during this period in the CsA-treated group ($P<0.05$). Furthermore, in the

TABLE 2. Time of CMV infection in the UGIT post-OLTx

Time post-OLTx (months)	CsA		FK506	
	No. patients endoscoped	CMV+	No. patients endoscoped	CMV+
1	26	3 (11.5%)	21	0 (0%)*
2	15	12 (80.0%)	26	9 (34.6%)*
3	4	3 (75.0%)	12	4 (33.3%)*
>4	20	0 (0%)	16	2 (12.5%)*
Total	65	18 (27.7%)	75	15 (20.0%)

* Statistically significant differences in percentage of patients with documented upper gastrointestinal CMV infection.

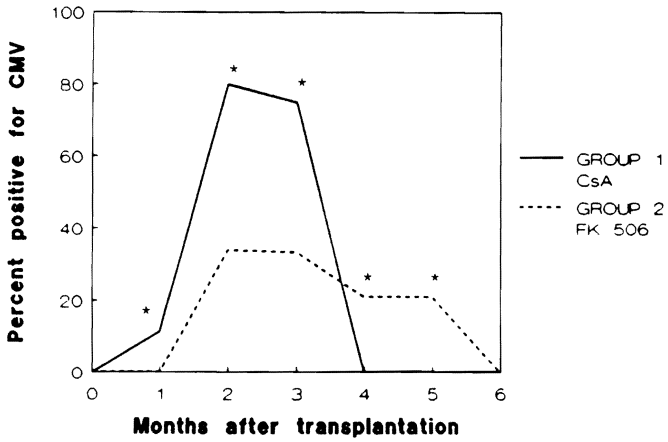

FIGURE 2. Point frequency of upper gastrointestinal CMV infection post-OLTx in CsA-treated patients (group 1) versus FK-treated patients (group 2) (*$P<0.05$) investigated at specific time points identified on the abscissa.

CsA-treated group, 80% and 75% of the patients who underwent endoscopy during the second and third months were found to have enteric CMV infection, as compared with 34.6% and 33.3%, respectively, in the FK-treated group. These differences were statistically significant ($P<0.05$). In those recipients who developed CMV enteritis, no difference was found between the two groups with regard to the donor-recipient CMV serologic status. The liver donors were seropositive in 77.8% (14/18) of patients treated with CsA, as compared with 80% (12/15) in patients treated with FK. Prior to transplantation, 15 patients of the CsA-treated group (23.1%) and 16 patients of the FK-treated group (21.3%) did not have antibodies to CMV in their serum. In both groups, over 90% of the seronegative recipients who received livers from seropositive donors developed CMV enteritis following transplantation.

In CMV-positive patients, by the time of upper gastrointestinal endoscopy, less than half of the FK-treated patients (7 out of 15) were still on steroid maintenance therapy, with a mean dose of 13.7±3.2 mg/day (range 5–30 mg/day), whereas all patients in the CsA-treated patients were on steroid therapy, with a mean dose of 20.6±1 mg/day (range, 10–30 mg/day) ($P<0.02$).

Enteric location of the CMV infection. Figure 3 shows the distribution of CMV infection in the upper gastrointestinal tract for both groups. In the two groups, the most common upper alimentary tract site found to be infected with CMV at any time was the stomach. The stomach was involved in more than 80% of the cases demonstrating upper gastrointestinal tract involvement in any organ within this system.

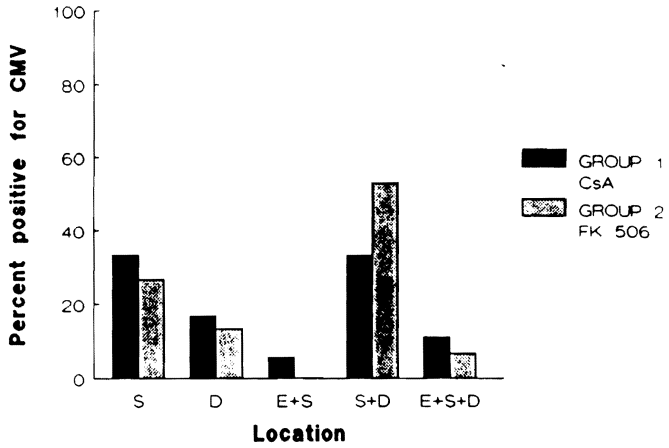

FIGURE 3. Location of CMV in the UGIT on patients of CsA (group 1) or FK506 (group 2) (E, esophagus; S, stomach; D, duodenum).

Morbidity of CMV infection. In both groups, patients experienced varying degrees of nausea, vomiting, and abdominal pain and discomfort with CMV enteritis. Another common presentation of CMV disease in both groups was fever (≥38°C) and chills with leucopenia (≤400/mm^3) and a typical lymphocytosis (>3%). In the CsA-treated patients, the mean duration of fever was 14±3 days as compared with 10±1.2 days in the FK-treated patients. A positive blood buffy coat was detected in 14 CMV-positive patients (77.8%) treated with CsA as compared with 11 CMV-positive patients (73.3%) treated with FK. In addition to CMV infection in the upper gastrointestinal tract, the disease involved multiple organs including the liver (3 patients), lungs (2 patients), both liver and lungs (2 patients), and sigmoid colon (one patient) in the CsA-treated group, as compared with only one case of combined CMV hepatitis and pneumonitis and two cases of CMV retinitis in the FK-treated group.

Survival. The overall 1-year patient mortality rate in the total study population was 8.6% (12 of 140). Of the eight deaths in the FK-treated group, only one patient was CMV-positive and died of disseminated CMV infection. The four deaths in the CsA-treated group were all CMV-positive. Three of these four deaths were related to CMV infection. The 1-year survival rates of CsA- and FK-treated patients are shown in Figures 4A and B. In the CsA-treated group, CMV-negative patients had a significantly higher 1-year survival rate (100.0%) than CMV-positive patients (77.8%) ($P<0.05$) (Fig. 4A). No significant difference in survival rates was observed between CMV-positive and CMV-negative cases (93.3% versus 86.3%, respectively) for the FK-treated group (Fig. 4B). The survival rates for CMV-positive patients in the two immunosuppression groups, although quite different, did not differ statistically. Four more patients in the CsA-treated group died during the second post-transplant year. Three of these patients were CMV-negative and one was CMV-positive.

CMV infection and OKT3 antirejection therapy. Thirteen patients in the CsA-treated group received OKT3 (20%) for a persistent rejection episode as compared with 13% (10 patients) in the FK-treated group (NS). Five of the 13 patients in the CsA-treated group developed CMV infection (38.5%) as compared with only two patients (20%) in the FK-treated group. This difference, however, was not statistically significant. No difference was found between patients who received OKT3 and

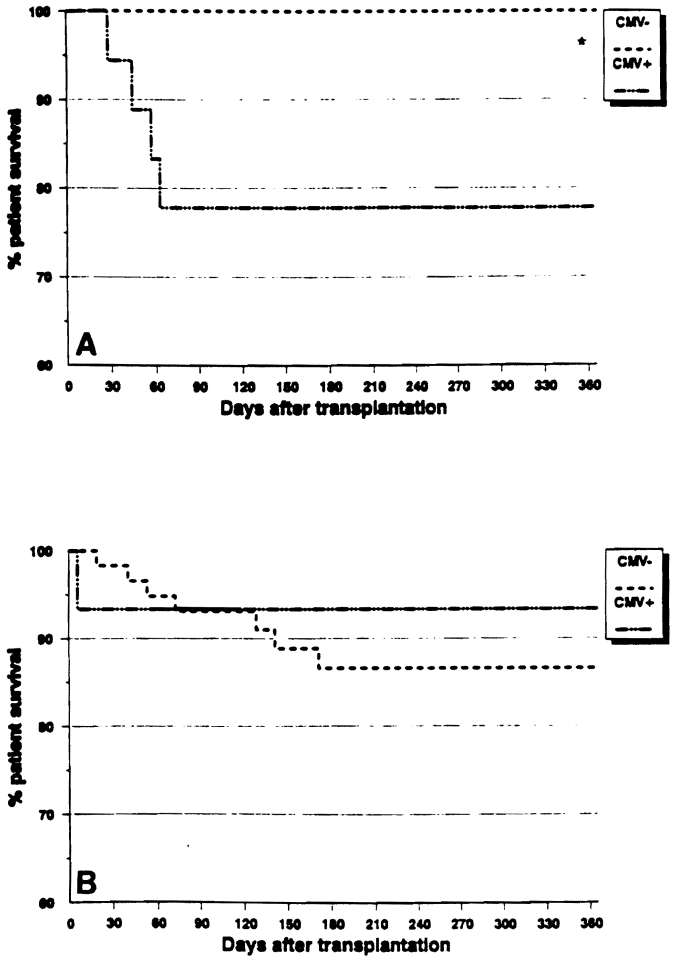

FIGURE 4. (A) Survival among CMV-positive and CMV-negative patients treated with CsA (*$P<0.05$). (B) Survival among CMV-positive and CMV-negative patients treated with FK506.

those who did not receive OKT3 in either group in terms of the time or location of CMV infection in the upper gastrointestinal tract post-OLTx. A potentially important finding is that CMV-positive patients on OKT3 in the CsA-treated group had a mortality rate of 40% (two of five) as compared with 0% (0 of 2) in the FK-treated group. Despite the apparently obvious difference between these two figures, this difference is not statistically significant, because the number of patients in each group who died was small. Moreover, it cannot be ascribed solely to the presence or absence of CMV infection, as a multivariate analysis assessing preoperative steroid and antibiotic use, blood product administration, the postoperative use of azathioprine, the postoperative steroid dose used, and the frequency of rejection episodes, as well as other variables, was not accomplished. Whenever identified, CMV infection was treated with gancyclovir in these patients.

DISCUSSION

In the present study, no association between the demographic variables of sex, age, or pretransplant liver diagnosis and the occurrence of CMV infection was evident in either group. Similar observations have been reported by others using CsA (*11*, *12*) and FK506 (*12*) as the primary immunosuppressive agent. The two groups also were comparable with regard to the location of CMV infection in the upper gastrointestinal tract of those found to have CMV infection (Fig. 3). The stomach was the most frequently involved site in both groups. The esophagus was the least often involved organ. This finding also agrees with earlier reports (*13*, *14*) and confirms the reduced incidence of CMV infection within squamous cell mucosal surfaces as compared with mucous-secreting mucosal surfaces (*15*, *16*).

Gastrointestinal involvement is a frequent manifestation of CMV infection in liver transplant recipients (*4*). Since the introduction of CsA into clinical organ transplantation, several studies have documented a lower incidence of symptomatic CMV infection in CsA-treated patients than that seen prior to the introduction of CsA (*17*, *18*).

With the introduction of FK506 into clinical liver transplantation at the University of Pittsburgh in February 1989 (*19*), the frequency of allograft rejection and the range of side effects experienced as a result of immunosuppression experienced in OLTx recipients have declined markedly (*8*).

Prior to transplantation, CMV infection was documented in the upper gastrointestinal tract of only one patient (0.7%). Gastrointestinal CMV disease has been described rarely in normal individuals (*13*) and is also known to occur occasionally in patients with advanced liver disease (*20*). Because of its ability to reactivate in patients receiving immunosuppression, an increased incidence of CMV infection has been seen in transplant recipients as compared with those studied prior to OLTx (*21*, *22*).

CMV disease is the most frequent infection experienced following liver transplantation (*11*, *23*). The upper gastrointestinal tract is the most frequent site of clinically evident CMV infection in organ transplant recipients (*24*). The present study demonstrates that patients on FK506 following OLTx have an overall lower rate of CMV infection than CsA-treated patients (20% versus 27.7%, respectively) (Fig. 1). This figure for the incidence of CMV infection in CsA-treated subjects is comparable to that reported by several other groups (*11*, *23*, *25*).

The critical period for CMV enteritis following OLTx is the first 2–3 posttransplant months (*4*, *11*). In the present series, during the first 3 post-OLTx months, CMV infection was significantly reduced in the FK-treated group as compared with the CsA-treated group ($P<0.05$) (Table 2 and Fig. 2). It is notable that no case of CMV enteritis was observed in the FK-treated group during the first postoperative month. The occurrence of CMV enteritis during this critical period is presumably a consequence of the intense immunosuppression required during this early period to prevent allograft rejection (*26*, *27*). In the present study, FK-treated patients had a reduced rate of early graft rejection and as a result they received less "other agent" immunosuppressive therapy. Both immunosuppression and rejection episodes per se have been shown to enhance the rate of CMV infections (*28*). The present data demonstrate that no case of CMV enteric disease was detected by the end of the fifth posttransplant month in either group during the subsequent 12–26-month period of follow-up (Fig. 2). This finding is consistent with the earlier reports that over 90% of the infections occurring later than 6 months following transplantation are bacterial (*11*). On the other hand, our data show no difference between the two groups in terms of the relationship between the occurrence of CMV enteritis and the donor-recipient serologic type. Further, our results show a high incidence (>90%) of primary enteric CMV infection in liver transplant recipients treated with either CsA or FK506. This

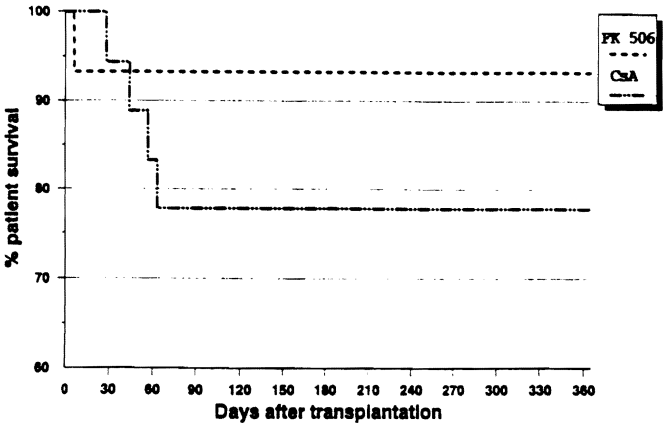

FIGURE 5. Survival curve of the FK- and CsA-treated groups.

finding is consistent with similar serological evidence that hepatic (*29*) and other major organ transplantation (*30–32*) is associated with transmission of CMV.

Based on the association of nausea, vomiting, and clinical evidence for gastric atony in patients with CMV enteritis, any transplant recipient manifesting these signs or symptoms probably ought to be endoscoped and biopsied to identify CMV disease before it becomes overtly evident or involves critical organs such as the liver or lungs.

The outcome of transplantation can be influenced by CMV infection (*11, 23, 33, 34*). In the present study, survival of CMV-positive patients on CsA (group 1) was significantly lower ($P<0.05$), at 12 months post-OLTx, than that of CMV-negative patients receiving CsA therapy (77.8% versus 100%, respectively) (Fig. 4A). In the FK-treated group (group 2), no significant difference in survival at 12 months post-OLTx between CMV-positive and CMV-negative patients could be demonstrated (Fig. 4B). When the survival rates of CMV-positive patients in the two groups were compared, the survival rate of FK-treated patients was not statistically different from that of the CsA-treated group (Fig. 5).

OKT3 antibodies provide a powerful means with which to treat steroid-resistant rejection episodes (*35*). Whereas some investigators have reported that patients who received OKT3 therapy have a greater incidence of CMV infections (*29, 36*), others have failed to find such an effect (*11, 25*). In the present study, a higher frequency of upper gastrointestinal CMV infection was associated with a higher mortality in the patients who received OKT3 in the CsA-treated group but not in the FK-treated group. Both groups were treated identically with ganciclovir once CMV enteritis was identified.

In summary, this study demonstrates that, following OLTx, upper gastrointestinal CMV infection appears later in FK-treated patients than in CsA-treated patients. Patients on FK have a significantly lower rate of CMV infection in the first 3 posttransplant months than do CsA-treated subjects. The stomach is the most frequently involved organ in the UGIT affected by CMV. In addition to CMV infection of the upper gastrointestinal tract, other organs were more involved in CsA-treated patients than in FK-treated patients. Patients who receive OKT3 therapy while taking FK506 do not appear at a higher risk of developing CMV infection. This differs from what is seen in CsA-treated patients. Finally, although gastrointestinal CMV infection continues to be a major cause of morbidity in liver transplant recipients, it is no longer a major cause of mortality. It is likely that CMV infections will be reduced further as improved immunosuppressive protocols are developed utilizing lower doses of FK506 than those currently being used.

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THE CORRELATION BETWEEN CYTOLOGICAL PATTERNS IN BILE AND HISTOLOGICAL FINDINGS IN LIVER TRANSPLANTATION[1]

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The cytological patterns in bile were compared with the histological findings in concomitant specimens from liver transplants. In cases where cytology showed a moderate (n=10) or high cell density (n=8), histology demonstrated rejection in 14 of 18 specimens and cholangitis in 4. When the cell density was low (n=22), histology was nearly normal in 3 specimens and showed cholangitis in 9, while rejection was observed in 10 specimens. Cell density in bile did not correlate quantatively with the severity of cellular infiltration in the portal triads or with the percentage of bile ducts attacked by inflammatory cells. The results of the present study support our hypothesis that an increased concentration of cells in bile is indicative of liver transplant rejection (sensitivity 58%), while normal cytology does not rule out the possibility of rejection (specificity 75%).

During the early postoperative phase, bile from liver transplants can be obtained at any time through a T tube or stent tube, and is therefore readily available for analysis. The color and volume of bile as well as the lipid composition (*1*) are clinically useful for evaluating liver transplant function. When it comes to the diagnosis of transplant rejection, although a change in the color and volume of the bile may raise clinical suspicion of rejection, the final diagnosis is usually based on the findings in a core needle biopsy or fine-needle aspiration biopsy (*2, 3*). However, because a core needle biopsy involves an invasive procedure, such material is usually not available for daily examination in the early postoperative phase (*4*).

At our institution, we have taken advantage of the availability of bile in these patients and, by applying the same methodology as for pancreatic juice cytology in pancreatic trans-

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