Digestive Diseases and Sciences, Vol. 39, No. 1 (January 1994), pp. 15–18

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Decreased Incidence of Viral Infections in Liver Transplant Recipients

Possible Effects of FK506?

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Cytomegalovirus (CMV) is a major infectious complication of organ transplantation and its incidence is influenced by the type and intensity of immunosuppressive therapy employed. Using a new immunosuppressive agent FK506, CMV infection was observed in 30% and CMV disease in 15% of the 26 liver transplant recipients. Delayed onset of CMV disease was noted; the mean time to the occurrence of CMV disease being 137 days posttransplantation. No graft loss or mortality could be attributed to CMV infection. Mucocutaneous herpes simplex virus (HSV) infections were encountered in 19% of the patients, while no disease could be attributed to varicella zoster virus or Epstein-Barr virus (EBV). The contribution of FK506 to a decrease in viral morbidity and associated mortality bears further investigation.

KEY WORDS: herpesvirus; cytomegalovirus; liver transplant; FK506.

CMV is a frequent source of morbidity and mortality after orthotopic liver transplantation (1, 2). The importance of immunosuppressive therapy in modulating the impact of CMV posttransplantation has previously been recognized (3). FK506 is a novel immunosuppressive agent that has been associated with less organ rejection and less early graft dysfunction (4). However, its impact on opportunistic viral infections is as yet uncertain. The newly established liver transplantation program at the Pittsburgh VA Medical Center allowed prospective assessment of consecutively transplanted patients receiving FK506 as primary immunosuppression. The purpose of this study was to evaluate the incidence and clinical characteristics of viral infections, in particular CMV infection in orthotopic liver transplant patients receiving FK506.

Manuscript received January 2, 1993; revised manuscript received April 1, 1993; accepted April 16, 1993.

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MATERIALS AND METHODS

Patient Population

The study population comprised 26 consecutive adult male patients who underwent orthotopic liver transplants at the Pittsburgh VA Medical Center between November 1989 and March 1991 and who survived at least 72 hr postoperatively. There were no exclusions. Their ages ranged between 28 and 65 years, with a mean of 46 years. Their diagnosis were cryptogenic cirrhosis (8), alcoholic cirrhosis (7), primary sclerosing cholangitis (5), non A, non B hepatitis (2), hepatitis B (2), primary biliary cirrhosis (1), and hemochromatosis (1). There was a total of three deaths. The duration of follow-up in the living patients ranged from 309 to 832 days, with a mean of 591 days.

Immunosuppression

All patients received 0.10 mg/kg of FK506 as a continuous drip over 24 hr until able to take oral medications. The oral dosage of FK506 was 0.15 mg/kg every 12 hr.

0163-2116/94/0100-0015$07.00/0

TABLE 1. INCIDENCE OF CMV INFECTION AND DISEASE IN LIVER TRANSPLANT RECIPIENTS

Preop CMV serology	*Number of patients*	*Number of patients with*				*Total number of symptomatic patients (%)*
		Infection (%)	*Viral syndrome*	*Localized CMV*	*Disseminated CMV*	
Negative	5	2 (40)	1	0	0	1 (20)
Positive	21	6 (28)	0	2	1	3 (14)
Total	26	8 (30)	1	2	1	4 (15)

Subsequent dosage adjustments were made as indicated by clinical course and FK506 plasma levels. One gram of methylprednisolone was given immediately after revascularization of the graft. Twenty milligrams of methylprednisolone was given intravenously immediately after transplantation and daily thereafter until the oral route was established, at which time 20 mg of prednisone was administered daily. During the subsequent months, prednisone was slowly tapered.

Antiviral Prophylaxis. High-dose oral acyclovir in dosages between 2400 to 3200 mg daily were used in three patients only. Four patients did not receive any acyclovir postoperatively. For the remaining 19 patients, the dosage of acyclovir ranged from 200 to 1600 mg daily.

Definition of Viral Infections

CMV Infection. CMV serology was determined using an enzyme immunosorbent assay (EIA) and titers ≥0.79 were considered positive. Primary infection was defined as isolation of virus or seroconversion in a patient who was seronegative before transplantation. Reactivation infection was diagnosed by isolation of virus in a seropositive recipient.

CMV Disease. Clinical diseases caused by CMV were the following types: viral syndrome, localized CMV disease, and disseminated CMV disease. Viral syndrome due to CMV required the following: (1) positive culture for CMV, (2) fever ≥38° C with no other source to account for it; and (3) one of the following findings: atypical lymphocytes ≥3%; white blood count ≤4000/mm^3, and platelets ≤100,000/mm^3. Localized CMV disease was defined as tissue invasion of a single organ determined histopathologically and by culture of the virus from tissue. Disseminated disease was defined as tissue involvement of two or more noncontiguous organ sites.

EBV. Antibodies against viral capsid antigen, early antigen, and Epstein-Barr nuclear antigen were determined preoperatively in all patients. Patients were defined as having a symptomatic EBV infection if they had EBV-associated lymphoproliferative disease by the presence of EBV DNA in tissue using nucleic acid hybridization. Antibody titers to detect asymptomatic rise were not routinely determined.

Herpes Simplex and Varicella Zoster. HSV infection was defined as presence of typical symptomatic oral or genital ulcers. For atypical lesions or those outside the genital or oral area, isolation of virus was also required. Varicella zoster virus infection was determined clinically by the presence of typical dermatomal lesions with or without viral isolation.

RESULTS

CMV Infection and Disease. Thirty percent (8/26) of patients developed CMV infection. These included two (40%) of the five seronegative recipients and six (28%) of the 21 seropositive patients (Table 1). Four of the eight infected patients were symptomatic. These included one of the two recipients with primary infection who developed CMV viral syndrome that resolved spontaneously. Symptomatic disease was also diagnosed in three of six patients with reactivation CMV infection. CMV gastritis (one patient), CMV retinitis (one patient), and disseminated CMV disease with hepatitis and colitis (one patient) were documented. All of these patients were treated successfully with ganciclovir.

Timing of CMV Infection. CMV infection occurred a mean of 80 days (range 23–225 days) after transplantation. Mean time to the onset of CMV disease was 137 days posttransplantation with a range of 65 to 220 days. Asymptomatic CMV shedding in urine or buffy coat was detected in three of four patients who eventually developed CMV disease. The time interval between first detection of CMV and onset of overt CMV disease was 14 days in the patient with disseminated CMV, 42 days in the patient with gastritis, and 195 days in the patient with CMV retinitis.

Relationship of CMV Infection to Recipient and Donor Antibody Status. Sixty-six percent (2/3) seronegative recipients with primary CMV infection received livers from CMV-seropositive donors, whereas, 0% (0/2) seronegative recipients who received livers from a CMV-seronegative donor developed CMV infection.

No definite association was found between the occurrence of reactivation CMV infection and serological status of the donor. The percentage of seropositive patients, 36% (4/11), who received livers from a CMV-seropositive donor was not significantly different from the percentage of patients, 20% (2/10), who received livers from a seronegative

donor ($P > 0.05$). All patients received random blood products that were neither screened nor selected for CMV antibody.

Rejection Episodes. Thirty-five percent (9/26) of the patients did not have any rejection episodes. Another 35% (9/26) received methylprednisolone (1-g bolus per patient) for suspected, but not biopsy-proven rejection. The remaining 31% (8/26) of patients had 10 episodes of biopsy-proven rejection. Of these 10 episodes, six were managed with adjustment of the baseline immunosuppression and four with a bolus of methylprednisolone, in addition to adjusting the baseline immunosuppression. No steroid recycles were given, and OKT3 was required in one patient only.

Graft Loss and Mortality. Overall, 11% (3/26) of patients died within the study period. Deaths occurred at 12, 25, and 42 days postoperatively. No evidence of CMV was present in patients who died. Likewise, none of the patients with CMV infection died.

Twenty-six study patients underwent 29 orthotopic liver transplants. Second transplants in two patients were performed at four and six days postoperatively, secondary to primary nonfunction of the transplanted allograft, and in the third patient 616 days postoperatively due to chronic rejection. Graft loss was not attributable to CMV infection in any of the patients.

Herpes Simplex. Nineteen percent (5/26) of patients experienced herpes simplex infections; all were mucocutaneous (orolabial) HSV infections. Mean time to onset was 82 days (range 10–223 days) postoperatively. Only one of the five patients with HSV infection was receiving acyclovir (200 mg every day) at the time of occurrence of HSV infection. All patients responded to oral acyclovir (1000 mg every day) with no evidence of dissemination.

Other Viral Infections. None of the patients developed varicella zoster infection or symptomatic EBV infection. Adenovirus was isolated from urine in an asymptomatic patient eight days postoperatively.

DISCUSSION

CMV has been recognized as the single most important contributor to posttransplant morbidity and mortality. Clinical presentation of CMV postoperatively varies from asymptomatic infection to fulminant disease. It is important to differentiate between CMV infection and CMV disease. CMV infection merely implies cultural or serologic evidence of viral replication, whereas CMV disease indicates the presence of specific symptoms attributable to CMV pathogenicity confirmed by laboratory evidence. CMV infection has been reported in 50–60% of the liver transplant recipients receiving cyclosporine, whereas clinically overt CMV disease is observed in 26–35% of the patients (1, 2, 5–7). The 15% incidence of CMV disease in our patients is the lowest reported in liver transplant recipients, to our knowledge.

An important factor influencing the incidence and course of CMV infection posttransplantation is the type and intensity of the immunosuppressive regimen employed. Lower incidence of CMV infection has been reported with the cyclosporine–prednisone than with the azathioprine–prednisone combination (8, 9). The exact basis for the lower incidence of CMV infection in our patients on FK506 remains to be determined. A possible contributory variable is lower adjunctive immunosuppression with FK506. Steroid recycles for rejection were not required in any patient and only one patient received OKT3 antibodies. A lower incidence of organ rejection has been previously documented with FK506 as compared to other immunosuppressive regimens (10, 11), thereby obviating the need for high-dose corticosteroid and antilymphocyte therapy. Both high-dose steroids and antilymphocyte preparations such as antithymocyte globulin and OKT3 are associated with an increased risk of CMV-related disease (2, 12). The lower incidence of CMV infection and disease is unlikely to be due to acyclovir, as 89% of the patients did not receive the high dosages shown to be effective in kidney transplants (13).

A noteworthy finding was the relatively late occurrence of CMV disease in our patients. Mean time to the onset of CMV disease in our patients was 137 days; when CMV retinitis, which is typically a late-occurring disease, was excluded, the mean time to the occurrence of CMV disease was still 100 days. In prior studies virtually all CMV disease occurred within the first six to eight weeks posttransplantation (2, 5, 14).

CMV disease is a significant contributor to graft loss and patient mortality. Prior to the introduction of ganciclovir, a mortality rate of 22% had been reported with CMV infection; the mortality with disseminated CMV disease being an astounding 66% (2). Stratta et al reported decreased mortality (6%) from CMV in liver transplant recipients with

the routine use of ganciclovir (5). No graft loss or mortality could be attributed to CMV in our study. Fewer overall infections (15), lesser need for retransplantation due to rejection, and routine employment of ganciclovir for treatment of CMV disease are some of the contributory variables to decreased mortality.

HSV infections were encountered in only 19% of the patients compared with 35% in cyclosporine patients in a previously reported study (2). The lower incidence may be due to oral acyclovir prophylaxis and sparing use of OKT3 in the study population. OKT3 and other antilymphocyte preparations have previously been associated with a higher incidence of symptomatic HSV infection (2, 16).

The results of this study must be interpreted with caution because of the relatively small sample size involved and the lack of concurrent controls. Nevertheless, a comparison of patients receiving FK506 from 1989 to 1991 with patients receiving cyclosporine between 1985 to 1987 (2) showed a notably lower incidence of herpesvirus infections, CMV disease, and mortality attributable to viral infections. It is uncertain whether our findings reflect any unique characteristics of FK506 or less intense additive immunosuppression along with FK506 or a lower net immunosuppression associated with improved technical and surgical standards. Given the recent introduction of FK506 into the transplant surgeon's armamentarium, these preliminary results appear highly promising and bear further investigation.

ACKNOWLEDGMENTS

We thank Shirley Brinker for preparation of the manuscript.

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