

# Impact of OKT3 Therapy on Cytomegalovirus and Herpes Simplex Virus Infections After Liver Transplantation

N. Singh, J.S. Dummer, S. Kusne, L. Makowka, T.E. Starzl, and M. Ho

**I**NFECTION with the herpes group of viruses, in particular, cytomegalovirus (CMV), is a significant cause of morbidity and mortality in organ transplant recipients. Immunosuppressive regimens containing anti-thymocyte globulin (ATG) have been shown to be associated with a higher frequency of symptomatic CMV disease.<sup>1</sup> Another anti-lymphocyte preparation, OKT3, is a murine monoclonal antibody that has proved efficacious in treating allograft rejection. The purpose of this study was to analyze the impact of OKT3 on the frequency and severity of CMV and herpes simplex virus (HSV) infections in adult liver transplant recipients.

## METHODS

The study population consisted of 121 consecutive adult patients who underwent orthotopic liver transplantation at our institution between January 1984 and September 1985, who survived for at least 72 hours postoperatively, and for whom preoperative serum samples were available. Standard immunosuppression consisted of cyclosporine (CsA) and corticosteroids (20 mg/d of prednisone). Rejection episodes were treated with additional steroids. Azathioprine (AzA) was usually administered to reduce the CsA dosage in patients experiencing nephrotoxicity. For more severe degrees of rejection OKT3 was administered.

CMV infection was diagnosed by virus isolation or by changes in serological titer (seroconversion or a fourfold or greater rise CMV antibody titer). Ninety-three patients were evaluable for CMV infection. Clinical diseases caused by CMV were of the following types: febrile viral syndrome, localized CMV disease, and disseminated CMV disease. HSV infection was defined as the presence of typical symptomatic oral/genital ulcers or histological evidence of tissue invasion. Ninety-five of 121 patients were seropositive for HSV antibodies pretransplant.

## RESULTS

Table 1 shows the relationship of symptomatic CMV disease to the immunosuppressives used. Thirty-two of 53 patients who received OKT3 developed CMV infection. Thirteen

(40%) of these developed symptoms, including seven with a viral syndrome and six with disseminated CMV disease. Five of six patients with disseminated CMV disease had primary CMV infection. Of 23 patients with CMV infection who did not receive OKT3, 14 (60%) were symptomatic, including nine with a viral syndrome and five with localized CMV disease. Thus the number of symptomatic patients among those who received OKT3 did not differ significantly from those who did not receive OKT3 (40% v 60%). However, disseminated CMV infection occurred in six (18%) of 32 patients who received OKT3 but in none of 23 patients who did not get OKT3 ( $P = .06$ ).

Of 95 recipients seropositive for HSV antibodies, 39 (41%) developed typical mucocutaneous HSV lesions including 29 patients with oral HSV and ten with genital HSV. Two patients developed HSV esophagitis, and two had HSV hepatitis. The group treated with OKT3 had more symptomatic illness due to HSV (22 of 54, 54%) as compared with patients who did not get OKT3 (13 of 41, 32%) ( $P = .05$ ).

## DISCUSSION AND CONCLUSION

Several studies have documented increased morbidity associated with CMV infection in renal transplant patients receiving ATG. Our data show that the frequency of overall symptomatic CMV disease was not influenced by OKT3. OKT3, however, appeared to increase

*From the Departments of Medicine and Surgery, University of Pittsburgh School of Medicine.*

*Supported in part by National Institutes of Health Grant 1R01 AI 19377.*

*Address reprint requests to M. Ho, MD, Crabtree Hall A427, University of Pittsburgh, Pittsburgh, PA 15261.*

*©1988 by Grune & Stratton, Inc.*

*0041-1345/88/2001-1241\$03.00/0*

Table 1. Relationship of Symptomatic CMV Disease to Additional Immunosuppression

Additional Immunosuppression	Total Evaluable Patients	No. Infected	No. Symptomatic	No. With Viral Syndrome	No. With Localized CMV Disease	No. With Disseminated CMV Disease
OKT3*	53	32*	13 (40%)	7	0	6†
No OKT3	40	23‡	14 (60%)	9	5	0
Total patients	93	55	27	16	5	6

\*All patients treated with OKT3 got additional steroids; 17 of 32 infected patients also received Aza.

†Proportion of patients with disseminated CMV disease treated with OKT3 compared with patients who did not receive OKT3 ( $P = .06$ ).

‡Twenty patients received additional steroids only, two received additional Aza only, and one patient did not receive any additional immunosuppression.

the risk of disseminated CMV disease, particularly in patients with primary CMV infection. These findings may help to identify patients at highest risk for severe or fatal CMV infection.

As reported in other organ allograft recipient groups, most HSV infections are due to reactivation of latent virus.<sup>2</sup> A few studies have correlated the use of antilymphocyte preparations with an increased risk of reactivation and symptomatic illness due to HSV. Similar data are not available for OKT3, but

we observed a higher frequency of symptomatic HSV infections in OKT3-treated, seropositive patients. Most of these were mucocutaneous infections and therefore not life threatening.

In conclusion, OKT3 treatment is associated with a higher risk of disseminated CMV infection, particularly in patients with primary CMV infection. It also increased the frequency of symptomatic HSV infection in HSV-seropositive liver transplant recipients.

#### REFERENCES

1. Bia MJ, Andiman W, Gaudio K, et al: Transplantation 40:610, 1985
2. Armstrong JA, Evans AS, Rao N, et al: Infect Immun 14:970, 1976

K. Ho

D  
histol  
unspe  
aspir  
oped  
trans  
exper  
tion a

Expe

Ran  
22 kg  
porto  
sion, f  
intra  
autotr  
mens  
14, 21  
detail  
ogy w

Clin

Tw  
liver  
prima  
sclero  
synth  
all ha  
or pa  
with  
first  
used  
mg/k  
week  
start  
perm

Trans