OKT3 and viral disease in pediatric liver transplant recipients

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Abstract: Seventy-four consecutive pediatric liver transplant recipients were reviewed to assess the effect of the monoclonal anti-T-lymphocyte antibody OKT3 on subsequent viral infection (9 patients were excluded due to postoperative demise during the 1st week). Twenty-two patients received OKT3 in addition to standard cyclosporine-prednisone immunosuppression for either steroid-resistant acute rejection (18) or to facilitate reduction of cyclosporine due to severe renal impairment (4). Invasive infections were diagnosed by histology or culture in tissue biopsies or bronchoalveolar lavage specimens. The overall incidence of viral infection was 58%, half of which was due to cytomegalovirus (CMV). Invasive viral disease was associated with increased mortality (37% vs. 3% $p=0.001$). Viral-related deaths were due to CMV (5), disseminated adenovirus (3), disseminated enterovirus (1) and respiratory syncytial viral pneumonia (1). The use of OKT3 was associated with increased viral disease (59% vs. 33% $p=0.04$) and invasive primary CMV disease (58% vs. 19% $p=0.04$). Trends were observed toward increased overall viral infection (73% vs. 51% $p=0.08$), primary CMV infection (58% vs. 25% $p=0.08$) and overall mortality (27% vs. 9% $p=0.08$) following OKT3 therapy. We conclude that pediatric liver transplant recipients who require OKT3 therapy may be at increased risk for invasive viral disease and especially invasive primary CMV disease.

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Viral infections, especially cytomegalovirus (CMV), are a significant cause of morbidity and mortality following solid organ transplantation (1–3). Renal (4–8) and cardiac (9) transplant recipients treated with antilymphocyte globulin and antithymocyte globulin have experienced an increased incidence of viral infections compared with patients receiving other immunosuppressive regimens. Similar data are unavailable for liver transplant recipients prior to 1980 due to limited overall survival in patients treated with the azathioprine-prednisone-antilymphocyte globulin regimen prior to the use of cyclosporine (10, 11). Antilymphocyte preparations have been used only sporadically following the dramatic success of liver transplantation with the cyclosporine-prednisone regimen. The recent introduction of the murine monoclonal anti-T-lymphocyte antibody OKT3 (Ortho Pharmaceutical, Raritan, NJ) proved to be highly effective in the salvage of steroid-resistant acute rejection of kidney, liver and heart transplants (12). The use of OKT3 in adult liver transplant recipients has recently been associated with an increased frequency of viral infections (13). The most recent report of viral infections in pediatric liver transplant recipients at this institution summarized data prior to the use of OKT3 (14). This study was performed to assess the effect of OKT3 therapy on subsequent viral disease in pediatric liver transplant recipients.

Materials and methods

Study population

The patient population consisted of all 74 consecutive pediatric patients (age 17 yr or younger) who underwent primary orthotopic liver transplantation at the Children's Hospital of Pittsburgh during the calendar year 1987. Patients who died either intraoperatively (2 patients) or within the first 7 postoperative days (7 patients) were excluded from evaluation, leaving a study population of 65 patients. None of the excluded patients received OKT3 and no evidence of viral infection was found at autopsy. Half of the 65 patients were less than 3 yr old. The mean age was 5.1 yr (standard devi-

ation 4.5 yr). Indications for transplantation included biliary atresia/hypoplasia (46), inborn errors of metabolism (6), cirrhosis (5), acute fulminant hepatitis (4), tumors (3) and sclerosing cholangitis (1). Forty-four patients had undergone previous abdominal operations, 37 of which were Kasai procedures.

All patients underwent orthotopic liver transplantation as described previously (15) either with a Roux-en-y choledochojejunostomy or, where feasible, primary end-to-end bile duct anastomosis with T-tube drainage. Matching of recipient and donor by CMV serologic status was not undertaken prior to transplant. Blood products were not routinely screened for evidence of CMV. The majority of blood transfusions were administered during the initial transplant operation.

The medical records of all patients were reviewed for the use of OKT3 as well as clinical and laboratory evidence of viral infections. Follow-up ranged from 6 to 18 months (mean 12 months) ending 1 July 1988.

Immunosuppression

Standard immunosuppression consisted of intraoperative intravenous cyclosporine (2 mg/kg) and methylprednisolone (500 mg) following reperfusion of the new liver. Intravenous cyclosporine (6 mg/kg/d) was administered postoperatively. Oral cyclosporine was added as soon as possible to maintain whole blood radioimmunoassay trough levels of 800 to 1000 ng/ml. Methylprednisolone was rapidly tapered during the postoperative period from 100 mg/d to 20 mg/d by decrements of 20 mg daily. Oral prednisone (20 mg/d) was begun as soon as enteral feedings were tolerated. The dose of prednisone was further reduced as dictated by clinical response. Occasional patients were begun on azathioprine when usual dosages of cyclosporine were associated with excessive side-effects such as nephrotoxicity or refractory hypertension.

Suspected acute rejection episodes manifested by transaminase and/or bilirubin elevation were treated empirically with 1 g intravenous hydrocortisone. Unresponsive episodes of acute rejection were diagnosed histologically by percutaneous needle biopsy revealing typical portal lymphocytic infiltrates with ductular invasion (16). Treatment consisted of a 5-d cycle of tapering dosage of intravenous methylprednisolone (100 mg/d down to 20 mg/d). Steroid-resistant rejection was then treated with a 14-d course of intravenous OKT3 (2 to 5 mg daily) and discontinuation of the steroid cycle (17). Additionally, 4 patients with severe renal impairment in the immediate postoperative period were given OKT3 to permit reduction of the cyclosporine dose.

Antibiotic prophylaxis

Ampicillin and cefotaxime (both at a dose of 100 mg/kg/d) were administered intravenously preoperatively and for the first 5 d postoperatively. Maintenance postoperative medications included oral nystatin (400 000 units every 6 hours) for fungal prophylaxis and trimethoprim-sulfamethoxazole (20–40 mg of trimethoprim daily) for prophylaxis of *Pneumocystis carinii* pneumonia. Intravenous immunoglobulin and acyclovir were not used prophylactically. Ganciclovir was administered on a compassionate use basis for biopsy-proven invasive CMV disease beginning in August 1987 and throughout the remainder of the study (approved by the Human Rights Committee of Children's Hospital of Pittsburgh).

Viral infections

Viral infections were diagnosed by either culture, serology or histopathology in combination with clinical observations. All donors were screened for CMV. Surveillance serologies for CMV, Herpes simplex virus (HSV) and Epstein-Barr virus (EBV), as well as viral cultures of buffy coat, throat and urine were obtained preoperatively when possible. Additional samples were obtained when clinically indicated. Viral cultures were performed as previously described (14). CMV serologies were initially performed by anticomplement immunofluorescence (18); more recently, CMV antibody was determined with a solid-phase immunofluorescence (19). Viral infections were considered invasive if the virus was demonstrated by either culture or histology in a tissue biopsy or bronchoalveolar lavage specimen. EBV-associated posttransplant lymphoproliferative disorders (PTLD) were diagnosed on the basis of histopathology and serology (20).

Statistical analysis

Observed proportions were compared with the Chi-square test or two-tailed Fisher's Exact Test for small samples. Calculated means were compared by Student's t-test. The hierarchical log linear model was used to examine the possible combined associations of OKT3 therapy, retransplantation and development of viral infection. This analysis was intended to generate models rather than to test a particular hypothesis (21) and was performed utilizing BMDP4F Software (BMDP Statistical Software, Inc. Los Angeles, CA).

Results

Viral infection

Fifty-three viral infections occurred in 58% (38/65) of patients. CMV accounted for half (26/53) of these episodes. The remainder were caused by HSV (7), respiratory syncytial virus (RSV) (5), adenovirus (5), rotavirus (4), EBV (3), parainfluenzae (2) and enterovirus (1). The mortality rate in patients with viral infection was 26% (10/38) compared to 4% (1/27) in patients who did not develop viral infection ($p=0.017$).

Thirty invasive viral infections occurred in 42% (27/65) of patients between 9 and 117 d following liver transplantation (mean 42 d). CMV was responsible for 70% (21/30) of these episodes. The remainder were caused by adenovirus (4), EBV (3), enterovirus (1) and RSV (1). The most frequent sites of visceral involvement were the liver (51%) and the lungs (30%). Mortality following invasive viral infection was 37% (10/27) compared with only 3% (1/38) for those who did not develop invasive infection ($p<0.001$). Nine deaths were directly due to complications of viral infection, including CMV pneumonia (3), CMV cerebritis (1), disseminated adenoviral hepatitis (3), RSV pneumonia (1) and combined enteroviral/polymicrobial sepsis (1). Another patient developed severe CMV pneumonia and hepatitis resulting in a rejection episode that necessitated retransplantation. This patient subsequently died of complications of retransplantation.

OKT3 was administered to 22 of the 65 patients in this study. The proportion of patients who developed viral infections following OKT3 therapy was greater than in those who did not receive OKT3 (73% vs. 51% $p=0.08$), as was the proportion of patients who developed invasive viral disease following OKT3 (59% vs. 33% $p=0.04$). An increased mortality rate was observed in those patients who received OKT3 compared with those who did not (27% vs. 9% $p=0.08$). The case-fatality rate of patients who developed invasive viral infection was similar for patients who received OKT3 and for those who did not (6/13 vs. 4/14, $p=0.35$).

Thirteen patients required retransplantation within 3 months of the primary liver transplant operation. The proportion of these patients who developed viral infections was greater than in the single transplant recipients (92% vs. 51% $p=0.016$). Similarly, invasive viral disease appeared to be more common in the retransplanted group compared with the single transplant group (69% vs. 36% $p=0.10$). Mortality following retransplantation was 31% compared to 11% after a single transplant ($p=0.11$).

The frequency of viral infection and invasive viral infection as a function of prior treatment with OKT3 and retransplantation was evaluated utilizing a hierarchical log linear model. The model that best fit these data for viral infections included independent effects of both OKT3 treatment and retransplantation, as well as interaction terms between OKT3 treatment and viral infections and retransplantation and viral infection; no interaction was found between OKT3 and retransplantation ($df=2$, likelihood ratio Chi-square $=0.80$, $p=0.67$). A similar model was found for invasive viral disease ($df=2$, likelihood ratio Chi-square $=3.8$, $p=0.15$). These models suggest that both treatment with OKT3 and retransplantation independently predict an increased risk of developing viral infection and invasive viral disease.

CMV disease

The overall rate of CMV infection was 40% (26/65); 81% (21/26) of these infections were invasive. Twenty-four percent (5/21) of invasive cases were fatal. The mean interval from transplantation to diagnosis of invasive CMV disease was 37 d (range 9–117) and this interval was not affected by the use of OKT3. Invasive CMV disease was diagnosed at a mean of 24 d (range 7–61) following administration of OKT3. The timing of OKT3 therapy following transplantation (mean 10 d) was not different among those patients who subsequently developed invasive CMV disease and those who did not. The mean interval from transplantation to diagnosis of CMV was longer in survivors compared with nonsurvivors (41 vs. 25 d, $p=0.05$).

CMV infection developed in 50% (11/22) of OKT3 recipients as compared to 35% (15/43) of untreated patients ($p=0.18$). Invasive CMV disease was more common among the OKT3 recipients compared with those who did not receive OKT3 (10/22 vs. 11/43, $p=0.09$). The case-fatality

Table 1. Effect of OKT3 on CMV infection following pediatric liver transplantation (numbers in parentheses are percentages)

	Pretransplant CMV serology			
	CMV-negative		CMV-positive	
	OKT3	no OKT3	OKT3	no OKT3
Total patients	12	16	2	5
CMV Infection	7/12 (58)	4/16 (25)	2/2 (100)	4/5 (80)
	$p=0.08$		NS	
Invasive CMV	7/12 (58)	3/16 (19)	2/2 (100)	3/5 (60)
	$p=0.04$		NS	
Case-fatality	3/ 7 (43)	1/ 4 (25)	0	0
	NS		NS	
Mortality	3/12 (25)	1/16 (6)	0	0
	NS		NS	

rate of patients who developed invasive CMV disease was similar for patients who had received OKT3 and for those who had not (3/10 vs. 2/11, p=0.05).

Adequate pretransplant serologic specimens for CMV were available from 35 of the 65 patients (Table 1). Eighty percent (28/35) were seronegative prior to transplantation. OKT3 therapy was associated with an increased overall incidence of primary CMV infection (58% vs. 25% p=0.08) and invasive primary CMV disease (58% vs. 19% p=0.04). Four deaths occurred following primary invasive disease. Clinical CMV infection occurred in 6 of the 7 patients who were seropositive prior to transplantation. Five of these patients developed invasive CMV disease but none of them died. OKT3 therapy did not appear to affect the CMV infection rate in this small group of patients. Techniques were not available to determine whether these infections represented reactivation of latent CMV or whether they represented new onset primary infections with different strains of CMV.

The omission of CMV serologic samples prior to transplant in 30 of the patients may result in a possible sampling error in the analysis of the effect of OKT3 therapy on CMV infection. The 35 patients from whom samples were obtained were comparable to those for whom samples were unavailable with respect to age (4.6 vs. 5.7 yr) and body size (16.1 vs. 19.4 kg). The first group was observed to have insignificantly increased rates of OKT3 therapy (14/35 vs. 8/30, p=0.38), invasive CMV disease (15/35 vs. 6/30, p=0.09), and mortality (8/35 vs. 3/30, p=0.30).

Only 1 patient received a liver transplant from a seropositive donor. She subsequently developed primary CMV hepatitis after a course of OKT3 but recovered satisfactorily following ganciclovir therapy.

Ganciclovir was administered to 12 of the 21 patients with invasive CMV disease, including 5 who died. The proportion of patients treated with ganciclovir was similar among patients who received OKT3 (60%) and those who did not (55%). The case-fatality rate was not altered by ganciclovir therapy among patients who received OKT3 (3/6) and those who did not (2/6).

Adenovirus

Adenoviral infections occurred in 5 patients, 4 of whom developed invasive disease. Three of the 4 received OKT3 and 2 had also been retransplanted. Hepatitis was present in all 4 patients with invasive infection. The 3 fatalities occurred in patients who developed disseminated infection with pneumonia. The serotypes in these patients were type 1 (2 cases) and type 2 (1 case). The serotype for the surviving patient with isolated adenoviral hepatitis, as well as an additional patient with a positive urine culture but no evidence of invasive disease, was type 5. An increased incidence of invasive infection with adenovirus was seen in those patients who received OKT3 compared with those who did not (14% vs. 2% p=0.11). Retransplantation was also associated with a trend towards a higher incidence of invasive infection (17% vs. 4% p=0.09).

Other viral infections

The incidence of HSV infection was similar between those patients who received OKT3 and those who did not (14% vs. 9%). Two of 22 patients treated and 3 of 43 not treated with OKT3 developed infection with RSV. One patient with RSV, who had received OKT3 and had also undergone retransplantation for a thrombosed hepatic artery, died of severe RSV pneumonia. A 2nd patient who had not received OKT3 developed an acute episode of croup severe enough to require intubation and was found to have a positive enzyme immunoassay for RSV. The remaining 3 patients with RSV infection had only mild symptoms. Three patients developed EBV-associated PTLD: 2 fatal cases occurred concomitant with invasive disseminated adenovirus in patients treated with OKT3 who had undergone retransplantation; 1 nonfatal case occurred in a patient with a single transplant who did not receive OKT3. One patient succumbed to disseminated enterovirus and polymicrobial sepsis following transmission of enterovirus from the donor liver.

Other factors

The role of antecedent and/or synergistic infection was evaluated in the 27 patients who developed

Table 2. Comparison of viral infections in adults and children following liver transplantation at the University of Pittsburgh

	Adults (13)	Children
Viral infection	53% (54/101)	58% (38/65)
Severe infection*	24% (24/101)	42% (27/65)
Case-fatality rate	37% (9/24)	37% (10/27)
Viral infection		
OKT3 therapy	76% (+)	73% (16/22)
no OKT3	46% (+)	51% (22/43)
significance	p<0.05	p=0.08
Severe infection		
OKT3 therapy	27% (+)	59% (13/22)
no OKT3	23% (+)	33% (14/43)
significance	p=NS	p=0.04

* "severe infection" in ref. 13 is defined similar to "invasive disease" herein.
+ not reported.

invasive viral disease. All but 4 patients acquired a total of 55 antecedent/synergistic infections, including 17 viral, 9 fungal and 29 bacterial. The sources of the bacterial infections were intra-abdominal (10), catheter-line sepsis due to coagulase-negative Staphylococcus (6), pneumonia (5) and various other sites (8). There was no difference in the frequency of antecedent/synergistic infections between those who had received OKT3 (27 episodes in 13 patients) and those who had not received OKT3 (28 episodes in 14 patients).

Abdominal surgery had been performed in 44 patients prior to transplantation. The incidence of invasive viral disease was similar for this group and for those who did not have prior abdominal surgery (19/44 vs. 8/31, $p=0.19$). Also, the mortality rate was similar for both groups (8/44 vs. 3/31, $p=0.49$). Among the 27 patients with invasive viral disease, the proportion with a history of prior abdominal surgery was the same for those who had received OKT3 and for those who had not (8/13 vs. 10/14). Previous abdominal surgery did not appear to affect the incidence of invasive viral disease or the role of OKT3 therapy on these infections.

Discussion

This study identifies the use of OKT3 as a significant risk for invasive viral disease and mortality in liver transplant recipients. Results from this study also demonstrate increased primary invasive CMV disease following OKT3 therapy in these patients. Complications arising from invasive viral disease accounted for nearly all the deaths beyond the 1st postoperative week in this series. Our results also suggest that retransplantation is associated with increased viral infection and invasive viral disease.

Table 3. CMV infection in liver transplant recipients at University of Pittsburgh (numbers in parentheses are percentages)

	Adults		Children	
	1981–83[24]	1984–85[25]	1983–84[14]	1987
Total patients	18	93	43	65
CMV infection	12/18 (66)	55/93 (59)	13/43 (30)	26/65 (40)
Invasive CMV	4/18 (22)	11/93 (12)	3/43 (7)	21/65 (32)
Case-fatality	4/12 (33)	12/55 (22)	1/13 (8)	5/26 (19)
OKT3 therapy	0	53/93 (57)	0	22/65 (34)
CMV serology	18	93	43	35
Seronegative	8/18 (44)	37/93 (40)	35/43 (81)	28/35 (80)
Primary CMV	5/8 (62)	17/37 (46)	6/35 (17)	11/28 (39)
Invasive CMV	2/8 (25)	8/37 (22)	2/35 (6)	10/28 (36)
Seropositive	10/18 (56)	56/93 (60)	8/43 (19)	7/35 (20)
Reactivation	7/10 (70)	38/56 (67)	7/8 (88)	6/7 (86)
Invasive	2/10 (20)	3/56 (5)	1/8 (12)	5/7 (71)

This study is limited by several methodological problems which could affect the clinical implications of the results. As a retrospective investigation, randomized controls were unavailable. The risk factors OKT3 and retransplantation are therapeutic options which were applied in a nonrandom fashion based upon clinical judgment. Further, it was not possible to control differences in the overall level of immunosuppression between patient groups. However, it was the practice of the transplant team to maintain similar doses and levels of immunosuppression in all patients. The size of comparison groups in this study was small, reducing the strength of our observations. Finally, the availability of only about half of the patients for pretransplant CMV serologic analysis may not be representative of the entire study population.

Occasional reports have described viral infection as a complication of OKT3 use following liver transplantation. In one randomized trial (22) of OKT3 compared to steroids for treatment of acute rejection in 28 liver transplant recipients, there was no significant difference in the rate of viral infection between the two groups (33% vs. 23%). In an earlier study (23) of 80 pediatric liver transplant recipients who received either OKT3 or steroid therapy for acute rejection, there were no significant differences between the two groups in the rates of viral infection, retransplantation, or mortality. A review (13) of 101 adult liver transplant recipients reported a higher overall viral infection rate following OKT3 therapy (76% vs. 46% $p<0.05$) but there was no difference in the incidence of severe viral disease (27% vs. 23%). In a comparison of viral infection rates between our pediatric patients and the adults reported by Kusne et al. (Table 2), the overall viral infection rates are about equal. However, there is a disproportionate increase in invasive viral disease within the pediatric population following OKT3 therapy.

CMV is the most common viral infection in liver transplant recipients (3). The results of four different series of pediatric and adult liver transplant recipients from this institution are summarized in Table 3 (14, 24, 25). The increased infection rate of invasive CMV seen in children following the introduction of OKT3 was not observed in adults. The differential effect of OKT3 on children may be accounted for by differences in the pretransplant CMV serologic status in these two groups of patients. Whereas only 20% of pediatric patients were CMV seropositive, 60% of adults were seropositive. Since only primary CMV disease appeared to be increased by the use of OKT3, it is not surprising that children were more adversely affected than adults. The comparatively low rates of CMV seropositivity among our pediatric recipients and do-

nors are reflective of the younger population (less than 3 yr old) from which the majority of these recipients (and donors) were drawn.

The major sources of transmission of CMV infections in transplant recipients are the donor organs and blood transfusions (1, 26–29). However, in a previous report (14) only 3 of 35 seronegative pediatric patients received allografts from seropositive donors; 1 of these subsequently developed CMV infection. In the current study only 1 donor was CMV-seropositive. This suggests that the major source of primary CMV infections seen in these two series was the administration of blood products. The risk of acquiring primary CMV infection from blood transfusions in children is 2.7% per unit (30). The average volume of packed red cells transfused intraoperatively during pediatric liver transplantation at this hospital was 10 units (31). Blood products were not screened for CMV antibodies during the study period. Based upon these data, our current policy is to use CMV-negative blood products in all seronegative pediatric liver transplant recipients.

Adenovirus is a known cause of approximately 5 to 10% of upper respiratory tract infections in the general pediatric population (32). Sporadic reports (33) have identified severe fulminant infection caused by adenovirus in immunocompromised hosts. A previous report (34) from this institution described a nearly identical incidence of adenoviral infections (8%) in 22 of 262 pediatric liver transplant recipients between 1981 and 1986. The current study provides further confirmation of the importance of adenovirus in pediatric liver transplant recipients and the possible impact of prior OKT3 therapy.

The identification of OKT3 therapy alone or in combination with retransplantation as a risk factor for increased morbidity and mortality from viral infections among pediatric liver transplant recipients with steroid-resistant acute rejection suggests the need for strategies to minimize its impact. It is unclear whether retransplantation may simply reflect the increased immunosuppression associated with a second induction (other than OKT3), or whether the second operation itself predisposes to infection. However, since there are no available alternatives to retransplantation, a cautious approach to the use of OKT3 is indicated. A biopsy which confirms rejection should be a prerequisite to the use of OKT3. The substitution of OKT3 for the usual steroid pulse-tapered cycle early in the course of acute rejection would eliminate any contributory component of additional steroids on the rate of infectious complications in this setting. The reduction of immunosuppression when a patient acquires one or both of these risk factors should be considered, recognizing that reduction of immunosuppression at the time of retransplantation may lead to rapid and severe rejection of the new allograft. However, in some centers the standard immunosuppression is often reduced or eliminated during the early course of OKT3 therapy (12). The risk of "rebound rejection" upon completion of OKT3 is reported to be high unless overall immunosuppression is returned to therapeutic levels during the last several days of this therapy (17). CMV prophylaxis is another option in patients who are receiving OKT3. Based upon recent optimistic reports describing anti-CMV therapy (35–40), the administration of anti-CMV immunoglobulin, acyclovir, or ganciclovir may be effective as a prophylactic strategy among seronegative liver transplant recipients who subsequently undergo a course of OKT3 and/or retransplantation.

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