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Infections in Pediatric Liver Recipients Treated for Acute Rejection

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MURINE MONOCLONAL antibody OKT3 (orthoclone OKT3), is a powerful immunosuppressant and has been shown to be very effective in reversal of acute rejection following kidney, liver and heart transplants.[1-3]

As with any kind of immunosuppression, one would expect that use of OKT3 might be associated with increased incidence of infections. However, there have been only a few detailed studies of infections following the use of OKT3 and even fewer comparing them to infections that occur when steroids only were the mainstay of anti-rejection therapy.[4,5] Hence we undertook a detailed retrospective review of infections that occurred in children receiving OKT3 for hepatic allograft rejection and compared them to infections that occurred in a similar group of children whose rejection was treated with steroids only.

PATIENTS AND METHODS

Eighty cases were reviewed from a group of pediatric patients having liver transplants at the Children's Hospital of Pittsburgh and the University of Pittsburgh between January 1981 and June 1986. To be included, patients should have received treatment for clinical or biopsy proven rejection within six months following the primary transplant and survived for at least seven or more days upon its completion. Patients were excluded if rejection therapy was aborted (<7 doses of OKT3 or less than 3 days of steroids in a five day oral recycle), or if they received polyclonal antilymphocyte globulin. Symptomatic infections were identified and grouped by strict adherence to predefined criteria. The study spanned two periods of rejection therapy. Until October 1984, study patients received only additional steroids to treat rejection. From October 1984, OKT3 became available to treat rejection either alone, or in addition to steroids. The patient's course was reviewed from the time of transplant, up to 180 days or 90 days after completion of rejection therapy whichever was longer. Data on pre-transplant characteristics, technical complications, infections, total amount of immunosuppression, retransplants and deaths were collected.

Statistical Analysis

Analyses were performed on a mainframe computer using a statistical program for social sciences (SPSS) for comparing proportions and student's t-test for comparing mean values. P values of <0.05 were considered significant.

RESULTS

Twenty-seven patients had rejection treated with only additional steroids. Fifty-three received OKT3 as part of their rejection treatment. The patient characteristics in both groups are outlined in Table 1.

Immunosuppression

Baseline immunosuppression was essentially similar in both groups and has been described in detail before.[6] Maintenance cyclosporine (CyA) and steroids were continued during OKT3 treatment. Twenty of twenty-seven patients in steroid group and 27/53 in OKT3 selected at random, had their total amount of intravenous and oral CyA, bolus steroids and prednisone calculated for the entire follow-up period as mean dose in mg/kg/day. These values shown in Table 1, showed no statistical significance between the groups.

Infections

The overall infection rate in the steroids only group was 66.6% (18/27). Viral infections occurred in 37% (10/27), fungal infections in 14.8% (4/27) and bacterial infections in 44.4% (12/27) of patients. Compared to this viral infections occurred in 45.2%, (24/53), fungal infections in 20.7% (11/53) and bacterial infections in 47.1% (25/53) of patients receiving OKT3. Two in the OKT3 group (3.7%) but none in the steroid group developed pneumocystis pneumonitis. These results are tabulated in Table 2. There is no statistically significant difference between the two groups either in the overall incidence of infections or in specific occurrence of viral, fungal or bacterial infections.

Technical Complications

In the steroid group, 9 patients (33%) had 12 technical complications whereas 18 in OKT3 group (34%) had 31 complications. The overall infection rates in both groups were the same (88.8%). The majority of the infections in this subgroup of patients were bacterial.

Retransplants and Deaths

Seven patients in the steroids group required 9 retransplants during the follow-up period. Approximately half of them (5/9) were for rejection. In the OKT3 group, 15 patients required 16 retransplants, 6/16 were for rejection. Three deaths occurred in the steroid group versus 11 in the OKT3 group. Two of the deaths in the steroid group and 9 of the deaths in the OKT3 group were directly attributable to infection. There was no statistical significance either in the rate of retransplants or deaths between the two groups.

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Table 1. Characteristics of the Patients Treated for Rejection

	Steroids Only (n = 27)	OKT3 (n = 53)
Mean age (months)	60	66
Sex males:females	13:14	26:27
Mean weight (kg)	16.4	19.7
Pretransplant (mean values)		
WBC/mm³	6.08	7.4
Total bilirubin mg/dL	18	18.1
Prothrombin time in sec.	16.1	16.8
Biliary atresia	55%	45%
Prior abdominal surgery	55%	56%
Immunosuppression given as mgm/kg/d (mean values)		
I.V. CyA	1.29	1.49
P.O. CyA	19.8	29.2
Bolus steroids	0.92	0.85
Oral prednisone	1.31	1.21
Mean follow-up days	171	161

Table 2. Various Infections Encountered in Patients Treated for Rejection

	Steroids Only n = 27	OKT3 n = 53
Total number of patients with infections	18 (66.6%)	36 (67.9%)
Patients with viral infections	10 (37%)	24 (45.2%)
Cytomegalovirus	3	10
Herpes simplex virus (HSV)	4	8
Adenovirus (AV)	1	4
Varicella zoster	1	1
Epstein-Barr virus (EBV)	1	4
Parainfluenza	—	1
Patients with fungal infections	4 (14.8%)	11 (20.7%)
Candida	3	10
Aspergillus	1	2
Nocardia	1	—
Patients with bacterial infections	12 (44.4%)	25 (47.1%)

DISCUSSION

Most of the reports describing the clinical use of OKT3 have dealt with its efficacy in reversing established allograft rejections.[1,2,7] The problems of infections had not been reported in detail. Since then a few reports have studied the topic of infections in renal recipients. Sanoh et al in their comparison of infections in 2 groups of renal recipients with acute rejection treated and not treated with OKT3 found higher incidence of viral and bacterial infections in the OKT3 group.[5] The number of cases with fungal infections were too small to compare.

In adult liver recipients receiving OKT3, Singh et al reported a higher incidence and more serious infections with herpes group of viruses.[4] However, the other patients in that report have not all been treated for rejection. In 51 consecutive pediatric liver recipients Breinig et al showed a different pattern of viral infections compared to adults.[8] Fewer of them had primary CMV and HSV infections. Adenoviral infections, not seen in adult liver recipients, were encountered.

Our study shows no difference in the overall rate of infections between the two groups of patients. This is still true even when individual categories of infections are considered separately (Table 2). Liver transplant patients also have higher incidence of fungal infections compared to other organ allograft recipients. This is probably related to higher incidence of technical problems and longer operative time in liver recipients.[9] Fungal infections also increase with increased amounts of steroids. The incidence of fungal infections in our two groups of patients were similar and were not statistically significant (14.8% in steroids versus 20.7% in OKT3).

Pediatric liver recipients have higher incidence of technical complications compared to adults.[10] These patients develop a variety of fungal and bacterial infections. The overall incidence of infections in patients with technical complications in the present series has been very high but it is the same in both groups.

In a report on hepatic retransplantation Shaw et al found that approximately 50% of retransplants in children were for rejection.[10] In our study retransplantation rate for rejection was 55% in the steroid group and 37.5% for OKT3 group, but was not significant statistically.

In conclusion, our present study shows that overall infection rate, rates of viral, fungal and bacterial infections and deaths secondary to infection were similar in groups of patients receiving OKT3 compared to patients whose rejection was treated with only steroids. The retransplantation rates for rejection were again not significantly different in the two groups.

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