739

Impact of ORTHOCLONE OKT3 on Liver Transplantation

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ADVANCES IN immunosuppression and refinements in surgical procedures have led to improved organ and patient survival in vascularized allograft transplantation. An increased understanding of allograft rejection mechanisms has made it possible to plan a rational program for developing and testing new reagents for the reversal of acute rejection. In the forefront of this generation of pharmaceuticals available for treating allograft rejection is the mouse anti-human T-cell antibody ORTHOCLONE OKT3 (Ortho Pharmaceutical Corp, Raritan, NJ).

In several clinical trials, Orthoclone OKT3, in conjunction with azathioprine and steroids, has demonstrated a marked ability to reverse established acute renal allograft rejection.[1-3] Clinical trials using this bioreagent in conjunction with cyclosporine (Cs) and steroids have recently been conducted[4] in an attempt to decrease the high rate of recurrent rejection seen in earlier trials using azathioprine and steroids.

We have previously reported the results of our pilot, randomized trial using Orthoclone OKT3 *v* high-dose steroids in conjunction with Cs and steroids for the treatment of acute hepatic allograft rejection.[4] This early study revealed a higher rate of reversal of rejection with Orthoclone OKT3 than with high-dose steroids. Using combined data from three transplant centers, Cosimi et al[5] subsequently confirmed our findings in their randomized clinical study of Orthoclone OKT3 *v* high-dose steroids for reversal of acute liver allograft rejection.[5]

In order to better define the conditions for Orthoclone OKT3 therapy during allograft dysfunction, we further expanded our studies to include 52 hepatic and ten renal allograft recipients.[6] Not only did we document the efficacy of Orthoclone OKT3 in reversing acute cell-mediated allograft rejection, but we found that the high incidence of recurrent rejection seen with azathioprine and steroids did not occur when Cs and steroids were used as baseline immunosuppression.

In the current report, an additional 105 patients were treated with Orthoclone OKT3 for acute hepatic allograft dysfunction. In addition to further analysis of the efficacy of Orthoclone OKT3 for reversal of acute hepatic rejection, we have analyzed the impact of Orthoclone OKT3 on liver transplantation at this institution by taking into account overall graft and patient survival.

MATERIALS AND METHODS

Case Material

One hundred fifty-seven hepatic allograft recipients received a course of Orthoclone OKT3 during the period from November 1984 to December 1985. Follow-up was available on all 157 patients up to April 1986. Statistical analyses of various parameters were obtained by comparing the study group with a control group consisting of 320 liver allograft recipients who received transplants during the period from August 1983 to December 1985 and who were not treated with Orthoclone OKT3.

Primary Immunosuppression

The principles of Cs and steroid therapy in the post-transplant period[7] and throughout the period of Orthoclone OKT3 therapy,[6] have been previously detailed. One major conclusion from our initial liver studies was that maintenance Cs and steroid therapy should be continued during Orthoclone OKT3 therapy, but that adjustments should be made in order to bring serum Cs up to a therapeutic level.

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Indication and Timing of Orthoclone OKT3 Therapy

The 157 hepatic allograft recipients were treated with Orthoclone OKT3 from one to 460 days after transplantation. Patients were stratified into three groups for analysis according to the period between transplantation and the initiation of Orthoclone OKT3 therapy as follows: group 1, Orthoclone OKT3 treatment started less than ten days postoperatively; group 2, Orthoclone OKT3 treatment started ten days to 3 months postoperatively; group 3, Orthoclone OKT3 treatment started more than 3 months postoperatively.

The rationale for this stratification was detailed in our previous reports[6] and will be briefly reiterated as to the current series of patients.

Group 1. Sixty-eight patients were started on a regimen of Orthoclone OKT3 therapy at a median of six days following transplantation. Forty-eight patients (71%) in this group had some histological evidence of rejection, with lymphoid infiltration on biopsy. In the remaining 20 cases (29%), the only apparent cause of hepatic allograft dysfunction in the immediate posttransplant period was ischemic injury or clinical primary graft nonfunction. In addition, 22 patients (32%) had concomitant evidence of renal impairment during the early posttransplant period, which precluded routine dosing with Cs.

Group 2. Among the 73 patients in this group, Orthoclone OKT3 therapy was started at a median of 19 days posttransplantation. Sixty-four (88%) of the patients had histological evidence of rejection with secondary deterioration of biochemical hepatic function parameters. In the remaining nine patients (12%), the primary cause of allograft dysfunction was determined to be cytomegalovirus (CMV) hepatitis (four patients), persistent ischemic injury (four patients), and biliary obstruction due to biliary anastomotic leakage (one patient).

Group 3. Orthoclone OKT3 therapy was started at an average of 420 days posttransplantation in the 16 patients in this group. These patients had no evidence of ischemic damage or renal failure. Percutaneous biopsy findings verified cell-mediated rejection in all patients, although the stigmata of chronic rejection were often present.

Table 1. Comparison of Nonsignificant Parameters Between Orthoclone OKT3-Treated and Control Groups

Parameter	Orthoclone OKT3-Treated	Control
Age (yr)	28.6	23.3
Sex (%)		
Male	43	45
Female	57	55
Presensitization (% PRA)	11.1	10.4
Degree HLA match	1.28	1.10

Values are expressed as means.

Orthoclone OKT3 Administration

The premedications and precautions used to diminish the side effects of Orthoclone OKT3 have not changed from the initial series.[6] Even with heightened physician awareness regarding the possibility of severe pulmonary edema due to preexisting fluid overload,[1,3] three of the 157 treated patients required intubation and pressor support. All three patients were successfully extubated following the brief support period.

Histopathological Criteria

One hundred forty (89%) of the 157 patients treated with Orthoclone OKT3 had a percutaneous liver biopsy performed before or shortly after starting Orthoclone OKT3 therapy. The biopsy specimens were processed and analyzed according to criteria previously described.[6] Eighty-five of the 140 patients who had pretreatment biopsies had repeat biopsies at the termination of Orthoclone OKT3 therapy or shortly thereafter.

Definition of Therapeutic Response

A complete response to therapy in the hepatic allograft recipients treated with Orthoclone OKT3 was defined as a return of liver function to normal or near normal during or within the first 2 weeks following completion of therapy. A partial response was defined as improvement of biochemical parameters, with or without objective histological improvement. Patients were assigned to the "no response" category if there was no improvement or worsening of biochemical parameters.

Statistical Methods

Fisher's exact test was used to determine the statistical significance of pretreatment parameters such as age, sex, degree of sensitization, and the degree of HLA matching between the treated and control groups. Life-table analyses were performed to determine both allograft and patient survival curves. A two-tailed P value of $<.05$ was considered statistically significant.

RESULTS

Patient Profile

Table 1 compares several parameters of the 157 Orthoclone OKT3-treated patients and the 320 control patients. Fifty-seven of the 157 liver recipients were in the pediatric age range of 6 months to 18 years, and averaged 6.8 ± 5.0 (SD) years. The average age for the

Orthoclone OKT3-treated group as a whole was 28.6 years *v* 23.4 years of age for the control group. One hundred thirty-five (86%) of the 157 patients were undergoing their first grafts; the other 22 (14%) had undergone retransplantation before receiving a course of Orthoclone OKT3.

All of the grafts used for hepatic recipients were selected without knowledge of the HLA types before transplantation. At the HLA A, B, and DR loci, the antigens matched averaged 1.28 ± 0.99 (range, 0 to 4; maximum of 6) *v* 1.10 ± 0.98 for the control group. The degree of presensitization, ie, percent reactivity against a random panel (PRA), was also not significantly different. The mean PRA was 11.1% for the treated group *v* 10.4% for the control group. Despite a positive T-cell crossmatch, the incidence of hepatic transplantation in the Orthoclone OKT3 treatment group was 13% as compared with 17% in the control group.

Response to Orthoclone OKT3 Therapy

In keeping with our initial findings,[6] the overall response rate of the 157 liver recipients treated with Orthoclone OKT3 was 79%, whereas 21% of those treated did not show objective improvement (Table 2). Eighty-five (54%) of those demonstrating a positive response to therapy had full reversal of biochemical abnormalities, whereas 25% had a partial response. The highest response rate was in group 2 patients, where the incidence of objective improvement was 88%. This group also had the best "full" response rate, with 69% of patients having resolution of all biochemical parameters of rejection.

In contrast, patients in group 1, whose therapy was initiated within nine days posttransplant, had only a 71% response rate, of which a "full" response was achieved in only 38% of the patients. The failure rate was 29%. Fifty percent of group 3 patients had a "full" response, whereas 19% had a partial response. The failure rate was 31%.

In order to better assess the response of hepatic allograft recipients with documented cell-mediated rejection to Orthoclone OKT3 therapy, we also analyzed group 1, 2, and 3 patients after eliminating a subset of patients whose graft dysfunction was ascribed exclusively to causes other than cell-mediated rejection. Twenty-nine such patients were identified, 20 (69%) of whom were in group 1, and nine (31%) in group 2. Of the 20 patients in group 1 with nonrejection graft dysfunction, 15 cases (75%) were due solely to ischemic injury during procurement, and five (25%) were due to primary nonfunction of the allograft. The causes of nonrejection graft dysfunction in the nine group 2 patients were previously listed under Materials and Methods.

Elimination of these patients from analysis improved, but did not significantly alter, the response rates of any group (Table 2). The overall response rate of the remaining 128 patients was 85%, with the "full," "partial," and "no response" rates being 58%, 25%, and 17%, respectively. The response rate of group 2 patients increased to 94%, with 72% having a "full" response and only 6% having "no response." The response rate of group 1 patients, who had evidence of cell-mediated rejection as the cause of allograft dysfunction, increased to 76%. Forty-three percent of these

Table 2. Percent Response Rates to Orthoclone OKT3 Treatment of Patients With Acute Hepatic Allograft Dysfunction

Group*	No. Patients	Response Rates (%)			
		Overall	Full	Partial	None
All groups-A	157	79	54	25	21
All groups-B	128	85	58	25	17
Group 1-A	68	71	38	33	29
Group 1-B	48	76	43	33	24
Group 2-A	73	88	69	19	12
Group 2-B	64	94	72	22	6
Group 3-A, -B	16	69	50	19	31

*A, analysis of all patients treated with Orthoclone OKT3 regardless of final determination of allograft dysfunction; B, analysis of the corresponding group of patients as in A, except for deletion of that subset of patients where there was no evidence of rejection.

patients had a "full" response, whereas only 24% were considered to be treatment failures.

Recurrence of Rejection and Impact on Retransplantation

During the follow-up period that extended until February 1986, only 25 (20%) of the 125 patients demonstrating a response to Orthoclone OKT3 therapy experienced further rejection episodes. The recurrent rejection episodes occurred a mean of 3.3 months and a range of 0.5 to 11.0 months following completion of Orthoclone OKT3 therapy. Sixteen (64%) of the 18 recurrent rejections were successfully treated with high-dose steroids, with return of normal hepatic function. Nine patients subsequently lost their grafts and required retransplantation.

The impact of Orthoclone OKT3, in conjunction with Cs and steroids, on the recurrent rejection rate is illustrated by the incidence of retransplantation. Among the control group, the incidence of retransplantation was 22.2%. This is in good agreement with our overall historical rates. Among all 157 patients treated with Orthoclone OKT3 for graft dysfunction, the incidence of retransplantation was 23.6%. Patients in group 2 had the lowest incidence of retransplantation, with only 12% requiring retransplantation. The retransplant rate in group 3 was 37%, whereas the rate of group 1 was 32%. When those patients with nonrejection causes of graft dysfunction were removed from analysis, the overall rate of retransplantation dropped to 15.9%. Thus, a total of 26 of the 29 patients in the subset of nonrejection-mediated allograft dysfunction required retransplantation. The corresponding decreased retransplantation rate in group 2 was 6.8%, whereas group 1 patients required retransplantation in 20.6% of cases.

Impact of Orthoclone OKT3 on Allograft and Patient Survival

A final consideration in evaluating a new immunosuppressive agent is the impact of the drug on overall allograft function and patient survival. Life-table analysis of allograft survival among control patients *v* patients treated with Orthoclone OKT3 for all patients with hepatic allograft dysfunction due to acute rejection is shown in Fig 1. During the entire posttreatment period, a statistically significant difference could be observed between the control group and the Orthoclone OKT3-treated group (Table 3). For the control group, the 6-month graft survival rate was 63%. In contrast, 80% of all allografts treated with Orthoclone OKT3 for graft dysfunction due to rejection continued to function at 6 months ($P < .005$). At 1 year, the corresponding figures were 55% and 64% for the control and treated groups, respectively ($P < .01$).

Although the parameters affecting patient survival are multifactorial,[8] one factor that has been linked to overall patient survival is rejection. Comparison of patient survival in the control group *v* the Orthoclone OKT3-treated group reveals a statistically significant improvement in the treated group at 6 months (74% *v* 83%, $P < .02$) (Fig 2). Although the data are not yet complete, there is a trend

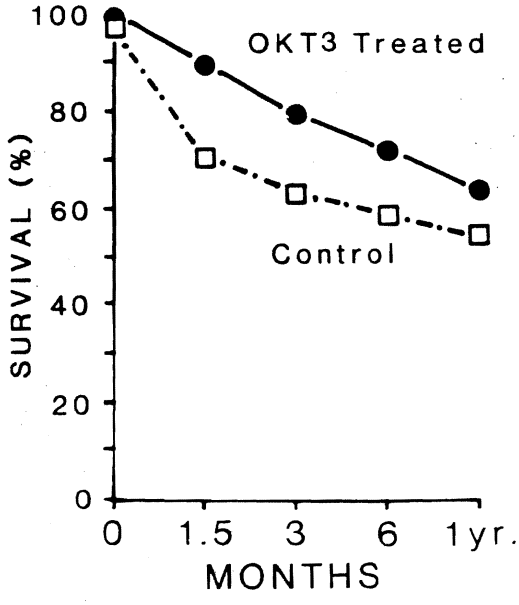

Fig 1. Comparison of allograft survival between control group (dotted line) and all patients treated with Orthoclone OKT3 for rejection (solid line). *P* values were <.01 for all time points, as determined by life-table analysis.

Table 3. Comparison of Allograft and Patient Survival Between Orthoclone OKT3-Treated and Control Groups

Group	Allograft Survival (%)		Patient Survival (%)	
	6 mo	1 yr	6 mo	1 yr
Control	63.4	55.0	73.7	71.6
Orthoclone OKT3-treated				
Overall	72.4 ($P < .003$)	64.4 ($P < .01$)	82.9 ($P < .01$)	75.2 (NS)
Group 1	54.1 (NS)	54.1 (NS)	72.1 (NS)	67.1 (NS)
Group 2	80.7 ($P < .003$)	76.7 ($P < .003$)	86.7 ($P < .005$)	79.2 (NS)
Group 3	68.8 ($P < .05$)	44.5 (NS)	81.2 (NS)	72.2 (NS)

Statistical comparison between patients with evidence of rejection treated with Orthoclone OKT3 and control patients. NS indicates that $P > .05$.

toward improved patient survival in the treated group *v* the untreated group at 1 year (72% *v* 75%, P = NS).

As indicated by the rate of reversal, the benefits of Orthoclone OKT3 treatment in group 2 patients with cell-mediated rejection persisted during the analysis of long-term graft and patient survival. Allograft function in group 2 patients was 81% (*v* 59% for controls, $P < .005$) at 6 months, whereas function at 1 year was 77% (*v* 55% for controls, $P < .005$) (Fig 3). Patient survival also appeared to improve during the same period. Overall, 87% of patients in group 2 were alive after 6 months (*v* 74% for controls, $P < .01$), and a definite, although statistically nonsignificant, difference was noted at 1 year (72% *v* 79% for controls and group 2 patients, respectively).

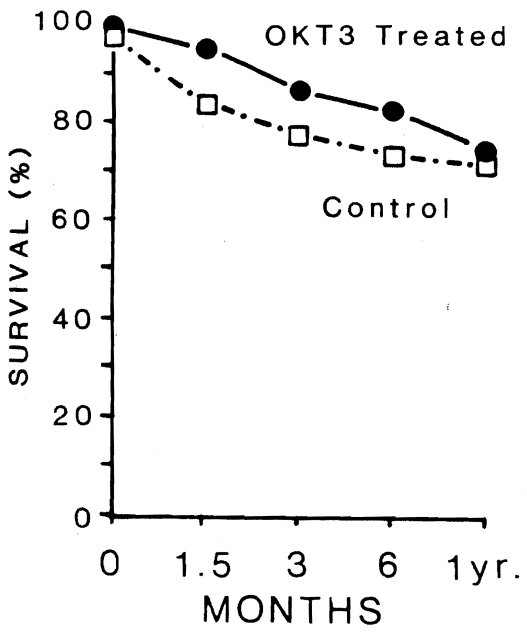

Fig 2. Comparison of patient survival between control group (dotted line) and all patients treated with Orthoclone OKT3 for rejection (solid line). *P* values were <.02 for all time points except for 1 year (NS), as determined by life-table analysis.

Group 1 patients constitute a subset of Orthoclone OKT3-treated patients with concomitant renal and hepatic dysfunction. Despite the historically poor prognosis of this group, these patients appeared to benefit from the use of Orthoclone OKT3 when rejection was involved in posttransplantation hepatic allograft dysfunction. Allograft function in the control group was similar to that of group 1 at the end of 1 year (55% *v* 54%, respectively) (Fig 3). In addition, normalization of patient survival of group 1 patients (67%) to that of the control group (72%) was noted.

Morbidity and Mortality

As we have previously reported,[9] it is often difficult to ascribe the death of a patient to any single given cause. Nevertheless, systemic

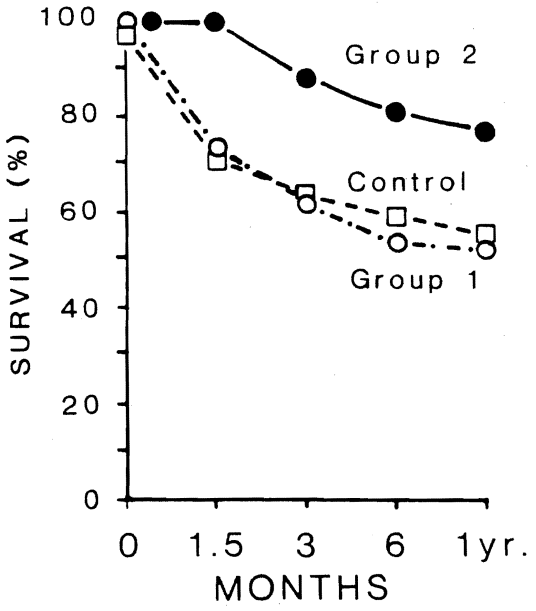

Fig 3. Breakdown of allograft survival curves between control group (dotted line, square dots) and group 2 patients (solid line) *v* group 1 patients (dotted line, round dots) treated with Orthoclone OKT3 for rejection. *P* values were <.003 for all time points when comparing group 2 and control curves.

sepsis accounted for 55% of deaths in the present study. This was generally due to the consequences of aggressive immunosuppression. Bacterial sepsis was predominant, followed by overwhelming fungal and viral infections. Unremitting cell-mediated rejection appeared to play a significant role in mortality in approximately 33% of these patients. Ischemic graft injury in the perioperative period, as well as primary graft nonfunction, were considered contributing factors in 28% of all mortalities, and occurred more often in group 1 deaths than in group 2 deaths (79% *v* 21%, respectively). Technical factors were involved in approximately 20% of mortalities, and included vascular thrombosis and biliary sepsis due to anastomotic breakdown. Finally, several miscellaneous causes of death were noted, including recurrent metastatic carcinoma (4%), cerebral vascular accident (8%), and myocardial infarction (4%). It should be noted that any combination of causes may have occurred in a given mortality.

Analysis of the morbidity associated with the administration of Orthoclone OKT3 to liver transplant recipients revealed a pattern similar to that previously reported.[6] Table 4 lists the incidence of side effects observed with Orthoclone OKT3. Hemodynamic instability in the form of transient changes in the BP or heart rate occurred most often. Fever, nausea, vomiting, diarrhea, dyspnea, and chills were also common. These adverse reactions appeared most frequently during the first few days of Orthoclone OKT3 therapy, presumably due to the release of vasoactive substances during T-cell destruction.[1,3] No deaths were directly attributable to these side effects.

Infectious complications, generally limited to acquired urinary tract infections, herpes zoster reactivation, and wound infections, were not considered major infections. Nevertheless, major infections occurred in 22% of treated patients and were often manifested as bacterial, fungal, or parasitic pneumonias, viral hepatitis, or systemic sepsis. In 56% of these patients, major infections played a role in mortality.

DISCUSSION

Orthoclone OKT3 is a murine monoclonal anti-human T cell antibody with clinically proven efficacy in the reversal of acute renal allograft rejection.[1-3] Although it has been approved by the Food and Drug Administration for reversal of acute renal allograft rejection, we have previously demonstrated that Orthoclone OKT3 is also efficacious in the

Table 4. Morbidity Associated With Orthoclone OKT3 Use

Side Effects	Patients (%)
Hemodynamic instability	77
Fever	70
Gastrointestinal disturbances	63
Dyspnea	41
Chills	31
Anaphylactoid reactions	2
Infections	
Major	22
Minor	45

reversal of hepatic allograft rejection.[4,6] The findings of our initial study, which have been verified by other centers,[5] suggest that the use of Orthoclone OKT3 in conjunction with Cs and steroids is associated with a high reversal rate of allograft rejection unaccompanied by the high incidence of recurrent rejection seen in the early studies. The purpose of this study was to analyze the long-term impact of Orthoclone OKT3 on hepatic allograft function as well as its effect on patient survival.

In agreement with our previous findings, Orthoclone OKT3 was shown to be effective in reversing acute hepatic allograft rejection. The rates of reversal for groups 1, 2, and 3 were similar to those previously reported.[6] In addition, this study verified our initial impression that patients who have the best response to Orthoclone OKT3 are those in whom cell-mediated rejection is the primary cause of postoperative liver allograft dysfunction. The less than optimal response rates seen in groups 1 and 3 reflect concomitant processes (ie, an element of coexisting ischemic injury and renal failure in group 1, and a degree of chronic rejection seen in group 3).

Cosimi et al[5] described their initial findings on the use of Orthoclone OKT3 in hepatic allograft rejection with a similar but more limited protocol. Specifically, treatment in their study was limited to patients who corresponded to our group 2 patients (ie, between seven and 30 days posttransplant). They report a full reversal of rejection parameters in 80% of the 25 patients studied. This is in good agreement with the 92% response rate and 72% full-reversal rate observed in our corresponding population.

Regardless of the good response rates seen in group 2 patients, it could be argued that the maximal benefit of this new immunosuppressive agent will be achieved in those patients who have done poorly historically. These patients manifest hepatic allograft dysfunction in the early posttransplant period and usually have a spectrum of metabolic derangements that make them poor operative candidates. Although Orthoclone OKT3 will not benefit those patients with hepatic dysfunction due to primary graft nonfunction or ischemic injury alone, we have demonstrated that it may help those patients with an element of rejection (in addition to coexisting renal failure) or ischemic injury. Graft function in this group of patients appears to normalize toward control figures following treatment.

One major impact of Orthoclone OKT3 on hepatic transplantation has been a low incidence of recurrent rejection following reversal of rejection. Approximately 20% of patients who had objective improvement in their rejection parameters had a subsequent rejection episode following completion of Orthoclone OKT3 therapy. Further immunosuppressive treatment successfully reversed 64% of recurrent rejection episodes, whereas the remaining 36% required retransplantation.

Because of the efficacy of Orthoclone OKT3 in the reversal of rejection, there appears to be a diminished requirement for retransplantation in those patients whose allograft dysfunction was caused by rejection. The major factor influencing retransplantation has been rejection.[10] The overall rate of retransplantation was 16%, as compared with 22% for the control group. The best results have been obtained in the subset of patients corresponding to those with acute rejection, namely, group 2 patients in whom the rate of retransplantation was 7%. This rate compares favorably with those figures reported by Cosimi et al,[5] who cited a retransplantation rate of 4% in their group of patients that roughly corresponded to our group 2 patients. The high rate of retransplantation (38%) seen in group 3 patients reflects the inability of Orthoclone OKT3 to reverse the stigmata of chronic rejection (ie, obliterative arteriolar lesions, loss of intrahepatic bile ducts, and portal fibrosis).[6] Nevertheless, Orthoclone OKT3 has been able to extend the functional use of group 3 allografts before the need for retransplantation.

The decreased need for retransplantation is also evidenced by the overall functional sur-

vival of hepatic allografts. Using life-table analysis, a statistically significant improvement in overall allograft survival could be demonstrated. The major benefit was seen principally in group 2 patients, whose graft survival increased by more than 20%. The allograft survival of group 1 patients approximated that of the control group.

Although patient survival is multifactorial, the most important parameter is the need for retransplantation. Thus, a reduced need for retransplantation should correlate with improved patient survival. Indeed, by life-table analysis, it appears that such a trend did exist. A statistically significant improvement in patient survival could be demonstrated in group 2 patients as compared with the control group at 6 months following completion of Orthoclone OKT3 therapy.

Long-term patient survival is also dependent on other parameters, such as vulnerability to infections. Although the majority of side effects associated with Orthoclone OKT3 therapy were acute but mild and largely limited to the duration of treatment, late-appearing infections with with *Pneumocystis carinii* and other opportunistic organisms, as well as viral hepatitis, may be related to a longer lasting effect of Orthoclone OKT3 on the immune responsiveness of the host. Although this is of only theoretical interest at present, a more detailed study will be needed to explore this issue.

The findings presented in this report suggest that Orthoclone OKT3 has favorably affected the overall success of liver transplantation in patients with documented liver allograft rejection with respect to both allograft and patient survival. The normalization of survival curves in group 1 patients suggests that Orthoclone OKT3 may also play a role in these critically ill patients, by adding a measure of treatment for early rejection and/or prophylaxis in patients in whom Cs therapy must be cautiously withdrawn or lowered. Thus, prudent use of Orthoclone OKT3 in conjunction with Cs and steroids has improved our ability to treat hepatic allograft rejection.

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