Transpl Int (2001) 14: 234–239

ORIGINAL ARTICLE

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Rabbit antithymocyte globulin versus OKT3 induction therapy after heart-lung and lung transplantation: effect on survival, rejection, infection, and obliterative bronchiolitis

Received: 10 February 2000
Accepted: 30 March 2001

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Abstract The superiority of different induction therapies after heart-lung and lung transplantation is not clearly established; specifically, whether monoclonal (OKT3) or polyclonal antibody induction therapy provides any advantage. Between 1989 and 1991 we used induction therapy with either rabbit antithymocyte globulin (RATG) or OKT3, given at random based on the availability of RATG. RATG was used in 25 patients (RATG group 1) and OKT3 in 38 patients (OKT3 group 1). Early results suggested a survival advantage with RATG. From 1992 until 1997 we used RATG induction therapy in 108 patients (RATG group 2). This study analyzed longer-term survival, infection, rejection, and obliterative bronchiolitis (OB) rates for RATG group 1 and OKT3 group 1 and assessed outcomes for RATG group 2. The 1-, 3-, and 5-year survival for RATG group 1 was 72%, 72%, and 52% and for OKT3 group 1 was 63%, 49%, and 34% ($P < 0.05$). The 1- and 3-year survival for RATG group 2 was 84% and 74%. The 1-, 3-, and 5-year actuarial freedom rates from lung rejection for RATG group 1 were 38%, 38%, and 31% and for OKT3 group 1 were 21%, 0%, and 0% ($P < 0.01$). The linearized rate (events/100 patient days) of all infections at 3 months was 1.55 ± 0.28 for RATG group 1 and 2.19 ± 0.27 for OKT3 group 1 (P = NS). The infection rate for RATG group 2 was 1.60 ± 0.13. The actuarial rates of freedom from OB at 1, 3, and 5 years for RATG group 1 were 84%, 51%, and 45% and for OKT3 group 1 were 77%, 61%, and 36% (P = NS), while for RATG group 2 the rates were 97% and 92% at 1 and 3 years ($P < 0.01$ vs RATG group 1 and OKT3 group 1). The use of RATG induction therapy from 1989 through 1991 resulted in improved actuarial survival and less rejection, without increased infection rates. The use of RATG since 1992 has continued to result in similar outcomes for survival, infection, and rejection. The time to onset of OB has improved further in recent years. This may be a result of recent improvements in cytomegalovirus (CMV) prophylaxis.

Keywords Heart-lung transplantation · Lung transplantation · Cytolytic induction therapy · Immunosuppression · Antilymphocyte antibodies

Abbreviations *CMV* Cytomegalovirus · *MALG* Minnesota antilymphocyte globulin · *OB* Obliterative bronchiolitis · *RATG* Rabbit antithymocyte globulin

Introduction

Lung transplantation is an established option in the therapy of end-stage lung disease [11]. Overall survival rates are improving, but remain inferior to the results achieved with other organ transplants [10]. Obliterative bronchiolitis (OB) is the major cause of late morbidity and mortality [2, 7] and is probably a result of chronic allograft rejection [25]. This emphasizes the importance of minimizing early rejection episodes [6, 17].

Antilymphocyte antibodies induce immunosuppression by several mechanisms and are amongst the most potent of the agents available in organ transplantation [8, 22]. There is, however, no consensus on whether cytolytic induction therapy should be used in lung transplantation. The major potential advantage is that induction therapy may reduce the incidence and severity of early lung rejection while cyclosporine levels are optimized. A recent meta-analysis of renal transplant patient-level data found a benefit of induction therapy versus no induction therapy on allograft survival [24]. We have adopted the use of cytolytic induction therapy after lung and heart-lung transplantation, believing that it decreases the incidence of early acute rejection and, thereby, the incidence of chronic rejection and OB [17].

The superiority of different types of induction therapy following lung transplantation has not been established; specifically, whether monoclonal or polyclonal antibody provides any advantage. We have used both monoclonal antibody (OKT3) and polyclonal rabbit antithymocyte globulin (RATG) induction therapy at our institution. The purpose of this review was to compare RATG versus OKT3 induction therapy after heart-lung and lung transplantation at Stanford University Medical Center.

Patients and methods

Patient selection and protocols

The study consisted of a retrospective review and analysis of patients who had undergone heart-lung, double-lung, or single-lung transplantation at Stanford. Patient information was obtained from the Stanford Transplant Database and a thorough review of clinical records.

Patient selection criteria were similar to those published elsewhere [14]. Acutely ill patients, including those on mechanical ventilation, were generally not considered [12]. Potential recipients were motivated and had suitable social support. Transplantation was not offered to patients with significant multisystem diseases or those with a recent history of malignancy.

Between January 1989 and December 1991, patients received RATG or OKT3 induction therapy at random, based on the availability of locally produced RATG. These patients are considered in two groups, hereafter termed RATG group 1 and OKT3 group 1, in this review. From January 1992, RATG was available at all times. A preliminary analysis of outcome was therefore undertaken, and this suggested that patients who received RATG induction therapy had an improved early survival and a greater early freedom from lung rejection [18]. As a result, all patients who had lung and heart-lung transplantation from January 1992 were given RATG induction immunosuppression. Patients receiving RATG cytolytic induction therapy between January 1992 and December 1997 are considered in a group termed RATG group 2 in this review. Complications of RATG infusion include rigors, fever, anaphylaxis, and occasionally hemodynamic compromise and circulatory shock. When patients developed intolerance at the onset of the slow infusion of RATG, the infusion was stopped and OKT3 induction therapy was given instead. Patients who received OKT3 induction for this reason between January 1992 and December 1997 are termed OKT3 group 2 in this study.

Postoperative care and immunosuppression

Monitoring and nursing routines were generally similar for all patients throughout the study period. Patients were actively diuresed, and fluid infusions were minimized in the early postoperative period, which often necessitated the use of vasopressor support. Patients were extubated when oxygenation was acceptable ($PO_2 > 80$ mmHg and $FiO_2 < 0.4$), hemodynamics were stable, bleeding had minimized, and they were awake. Prophylactic ganciclovir and CytoGam were given when either the donor or recipient were cytomegalovirus (CMV)-positive [21].

Triple-drug maintenance immunosuppression was used throughout the study period. Cyclosporine was commenced 12 to 24 h after transplantation once hemodynamics and urine output were stable. The target level was 150–200 ng/dl by postoperative day 7. Azathioprine was given at 2 mg/kg per day following initial loading with 4 mg/kg in the operating room. Maintenance dosages were guided by the white blood cell count. Methylprednisone was given at a dose of 500 mg in the operating room, and then 125 mg every 8 h for the first 24 h. Steroids were then withheld for 2 weeks to allow bronchial healing when oral prednisone was started at a dose of 0.6 mg/kg in two divided doses. Steroids were weaned over a period of 3–4 weeks to a maintenance dose of 0.2 mg/kg per day.

The protocol for monoclonal OKT3 induction therapy consisted of 5 mg/day on postoperative days 1–7. The protocol for RATG consisted of 2.5 mg/kg per day on postoperative days 1, 2, 3, 5, and 7. The duration of induction therapy was therefore similar for the two cytolytic agents. Patients received premedication with hydrocortisone, Benadryl, and Tylenol 30 min prior to the first three infusions. Once patients were ambulatory and tolerating a normal diet, they were discharged from the hospital.

Follow-up

Patients were followed by the Heart-Lung/Lung Transplant Service. They were seen twice a week for the first 3 weeks, and then weekly for another 4 weeks. Consultations were then spaced according to progress. Patients remained at the Stanford Home-tel to receive ambulatory treatment for the first 3 months, after which consultations were spaced according to progress. Longer-term follow-up consultations were undertaken at least once a year, but usually about once every 6 months. Surveillance bronchoscopies were undertaken at 2, 4, 8, and 12 weeks, and then at 6 months and 1 year. Pulmonary function tests, a chest radiograph, and arterial blood gas evaluations were done at each clinic visit or when clinically warranted.

Table 1 Demographics and perioperative data. Comparisons are of patients in RATG group 1 and OKT3 group 1 vs RATG group 2 and OKT3 group 2. Differences in age, weight, height, and times analyzed by two-tailed *t*-test; differences in gender and diagnosis analyzed by Pearson's χ^2-test. Data expressed as mean ± SD (*RATG* rabbit antithymocyte globulin, *NS* not significant)

Variable	RATG group 1 (1989–1991)	OKT3 group 1 (1989–1991)	RATG group 2 (1992–1997)	OKT3 group 2 (1992–1997)	Comparison (1989–1991 vs 1992–1997)
Number of patients	25	38	108	21	
Age (years)	31 ± 13.7	31 ± 15.7	28 ± 12.7	33 ± 14.8	NS
Weight (kg)	53 ± 17.3	52 ± 26.6	59 ± 14.1	54 ± 14.5	NS
Height (cm)	161 ± 26.5	150 ± 38.3	164 ± 16.7	160 ± 14.3	NS
Gender (M/F)	9/16	25/13	63/45	12/9	NS
Heart-lung/Lung	18/7	20/18	44/64	11/10	NS
Waiting time (days)	244 ± 245	181 ± 177	406 ± 291	526 ± 264	$P < 0.05$
Ischemic time (min)	178 ± 72	200 ± 57	254 ± 80	251 ± 71	$P < 0.05$
Length of stay (days)	31 ± 24	39 ± 33	27 ± 40	27 ± 32	NS

Statistical analysis

Numeric results are expressed as mean ± standard deviation. Continuous variables were analyzed by two-tailed *t*-test and discrete variables by continuity-adjusted χ^2-testing. Actuarial life-table data were calculated by the Cutler-Ederer method. Time-related event-free rates are reported from actuarial estimates as the mean ± standard error. Comparison between actuarial curves was made by the Gehan method. The linearized rate of events was calculated as the number of events occurring per 100 patient days.

Results

Between January 1989 and December 1991, a total of 63 patients had lung or heart-lung transplantation with postoperative cytolytic induction immunosuppression. Of these, 38 (20 heart-lung, 18 lung) received OKT3 (OKT3 group 1) and 25 (18 heart-lung, 7 lung) received RATG induction therapy (RATG group 2). Between January 1992 and December 1997, a total of 129 patients had lung or heart-lung transplantation with cytolytic induction immunosuppression. Of these, 108 (44 heart-lung, 64 lung) tolerated RATG induction therapy (RATG group 2). The remaining 21 patients (11 heart-lung, 10 lung), who developed adverse reactions to RATG, received OKT3 (OKT3 group 2). Pretransplant patient demographics and perioperative data are shown in Table 1. The groups were generally comparable in terms of age, gender, preoperative diagnosis, height, and weight. Mean waiting times for transplantation were longer in the groups with more recent transplantations (RATG and OKT3 groups 2) than they were in the earlier 3 years ($P < 0.05$). Ischemic times for organ insertion also tended to be longer in recent years ($P < 0.05$), reflecting an increased number of more distant procurements. Length of hospital stay tended to be similar during the review period.

Actuarial survival rates are shown in Fig. 1 for the RATG groups and OKT3 group 1. Longer follow-up data were available for the groups of patients that underwent surgery between 1989 and 1991. Survival rates at 1, 3, and 5 years were 72%, 72%, and 52% for RATG group 1 and 63%, 49%, and 34% for OKT3 group 1 ($P < 0.05$). The actuarial survival rates for RATG group 2 at 1, 3, and 5 years were 85%, 74%, and 74% ($P < 0.01$ vs OKT3 group 1; P = NS vs RATG group 1). The actuarial survival rates for OKT3 group 2, which are not plotted in Fig. 1, at 1, 3, and 5 years were 76%, 52%, and 39% (P = NS vs RATG group 2).

Actuarial rates of freedom from lung rejection (Fig. 2) at 3 months, and 1, 3, and 5 years in RATG group 1 were 48%, 38%, 38%, and 31%, respectively, and in OKT3 group 1 were 26%, 21%, 0%, and 0% ($P < 0.05$). Actuarial rates of freedom from lung rejection at 3 months, and 1, 3, and 5 years in RATG group 2 were 69%, 63%, 56%, and 56%, respectively ($P < 0.01$ vs OKT3 group 1; $P < 0.05$ vs RATG group 1). Actuarial rates of freedom from lung rejection at 3 months, and 1, 3, and 5 years in OKT3 group 2 (not shown) were 44%, 38%, 38%, and 38%, respectively ($P < 0.05$ vs RATG group 2).

Actuarial rates of freedom from biopsy-proven OB are shown in Fig. 3. Rates of freedom from OB at 1, 3, and 5 years in RATG group 1 were 84%, 51%, and 45%, respectively, and in OKT3 group 1 were 77%, 61%, and 36% (P = NS). Actuarial rates of freedom from biopsy-proven OB at 1 and 3 years in RATG group 2 were 97% and 92%, respectively ($P < 0.01$ vs OKT3 group 1; $P < 0.01$ vs RATG group 1). Rates of freedom from OB at 1 and 3 years in OKT3 group 2 (not shown) were 93% and 57%, respectively ($P < 0.01$ vs RATG group 2).

Linearized infection rates at 3 months for bacterial, viral (CMV), and overall infections for the RATG groups and OKT3 group 1 are shown in Fig. 4. Comparisons generally did not reach statistical significance, the exceptions being the viral infection rate of OKT3 group 1 versus RATG group 2 ($P < 0.05$) and the bacterial in-

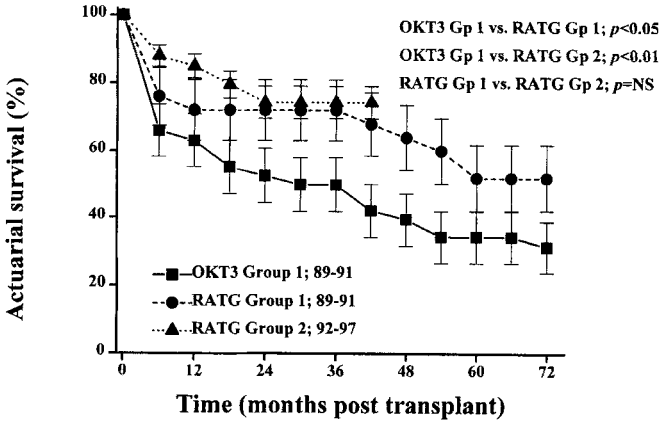

Fig. 1 Comparison of actuarial survival rates for rabbit antithymocyte globulin (*RATG*) induction therapy groups and for OKT3 group 1. Time-related event-free rates are mean ± standard error. Differences between the curves were calculated by Gehan testing

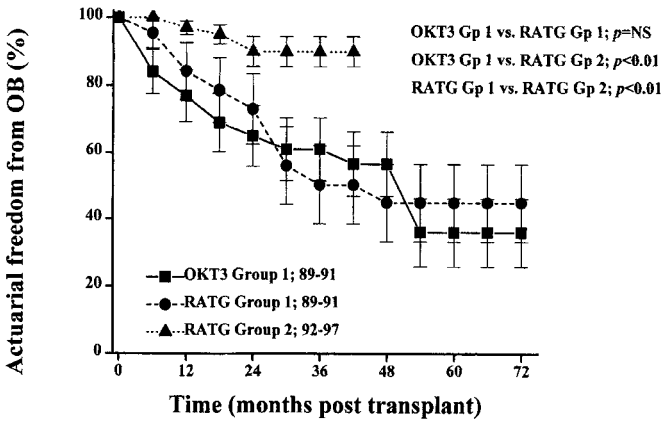

Fig. 3 Comparison of actuarial freedom from biopsy-proven obliterative bronchiolitis (*OB*) for rabbit antithymocyte globulin (*RATG*) induction therapy groups and for OKT3 group 1. Time-related event-free rates are mean ± standard error. Differences between the curves were calculated by Gehan testing

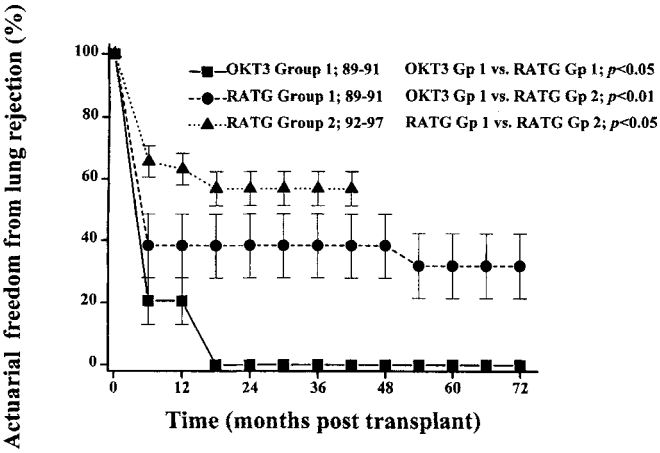

Fig. 2 Comparison of actuarial freedom from lung rejection for rabbit antithymocyte globulin (*RATG*) induction therapy groups and for OKT3 group 1. Time-related event-free rates are mean ± standard error. Differences between the curves were calculated by Gehan testing

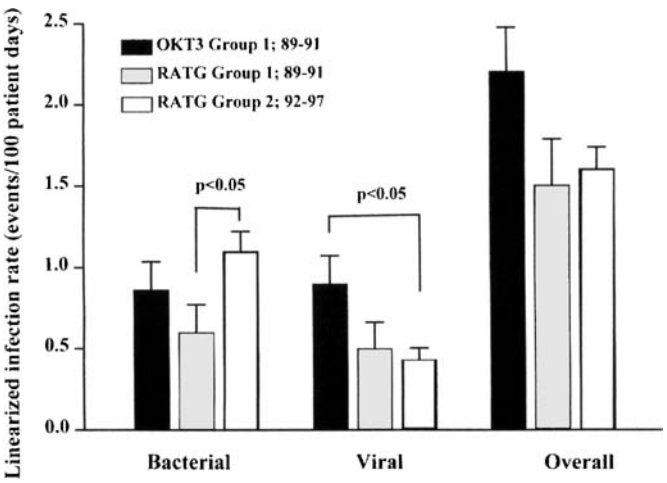

Fig. 4 Linearized rates (events/100 patient days) of bacterial, viral (CMV), and overall infections for rabbit antithymocyte globulin (*RATG*) induction therapy groups and for OKT3 group 1. Differences were compared by continuity-adjusted χ^2-testing

fection rate of RATG group 2 versus RATG group 1($P < 0.05$). Linearized bacterial, viral, and overall infection rates for OKT3 group 2 (not shown) were 0.75 ± 0.22, 0.49 ± 0.18, and 1.74 ± 0.33, respectively (all P = NS vs RATG group 2).

Discussion

Between 1989 and 1991 we used OKT3 or RATG cytolytic induction therapy after heart-lung and lung transplantation, given at random based on the availability of locally produced RATG. Survival and long-term pulmonary function benefits were achieved in our patient population, regardless of the type of induction therapy employed. When RATG was consistently available, a preliminary analysis of outcome suggested that patients receiving RATG had an advantage both in terms of survival and freedom from early rejection [18]. The present review, with longer-term follow-up than the preliminary study, confirms these advantages in the group receiving RATG. It also finds that patients who received RATG in the 5 years from 1992 have similar improved survival rates. An even longer latency period in time to onset of OB has been achieved in patients undergoing transplantation in the last 5 years compared to

the 3 years before that. This is possibly a consequence of recent, more aggressive anti-CMV prophylaxis and treatment. Our policy of ganciclovir and CytoGam prophylaxis was instituted during 1990 and would not have affected all the patients in the early groups in this study [21]. It is not clear why patients undergoing transplantation after 1992 showed less lung rejection than those operated on before 1992, who also received RATG induction therapy, since maintenance immunosuppression remained the same. One possible explanation is that lung reperfusion injury was under-diagnosed in the early part of this series and was incorrectly recorded as rejection in the Transplant Database. We have had relatively little experience with OKT3 induction therapy after lung and heart-lung transplantation since 1992. The 21 patients who received OKT3 induction therapy did so because of adverse reactions to RATG and any comparisons of outcome with this patient group should therefore be treated with caution. Nevertheless, the data seem to confirm an apparent tendency for earlier rejection episodes and earlier onset of OB with OKT3.

Both monoclonal OKT3 antibody and polyclonal RATG induce a rapid and profound lymphocytopenia [1]. There are probably several mechanisms involved, including complement-dependent cytolysis, cell-mediated antibody-dependent cytolysis, as well as opsoniztion and macrophage induced phagocytosis [1]. OKT3 is directed against the CD3 complex of all T cells with this receptor. RATG, on the other hand, contains a mixture of multiple antibody specificities, which account for complex functional effects. RATG also reacts strongly with B cells, monocytes, macrophages, and platelets, depending on the immunogens used in the immunization [1]. Different batches of RATG may vary for the same reason. The effects of RATG are therefore not restricted to the T cells, and this may explain some of the differences in outcome found in the present analysis.

Some groups advocate an immunosuppressive regimen without cytolytic induction therapy because of concerns about promoting fungal and viral infections, especially CMV [13, 15]. An increased incidence of lymphoproliferative disorder has been reported in cardiac transplant recipients after immunosuppression with OKT3 [23]. There are also significant cost factors associated with cytolytic induction agents. We have not adopted this approach, believing that induction therapy decreases the incidence of acute rejection and, thereby, the incidence of chronic rejection and OB [17]. Another potential advantage of using induction therapy is that cyclosporine levels can be established gradually while minimizing nephrotoxicity, which may be particularly important if cardiopulmonary bypass was necessary. Survival and freedom rates from OB in this review compare very favorably with data available from the Registry of the International Society of Heart and Lung Transplantation, without any significant increase in the risk of infection [10]. In renal allograft studies, individual randomized trials comparing induction therapy with conventional immunosuppression alone failed to show that induction therapy has benefit with regard to allograft survival [16, 20]. However a meta-analysis of individual patient-level data showed a benefit in graft survival at 2 years, especially in presensitized patients [24]. One preliminary report in the lung transplant population found a reduced incidence of OB at 2 years with cytolytic induction therapy versus conventional triple-drug immunosuppression [4]. A 1993 review of institutions in the United States which perform heart-lung and lung transplantation found that approximately 90% advocate cytolytic induction therapy [5].

There is also no consensus regarding the optimal induction agent or regimen. Indeed, the same review of lung transplant centers found that of the 90% questioned who opted to use induction therapy, approximately half favored OKT3 and the other half various polyclonal antithymocyte globulin preparations [5]. One study which compared induction therapy with OKT3 ($n = 11$) versus Minnesota antilymphocyte globulin (MALG; $n = 13$) found longer latencies for OB with OKT3 [19]. However, the OKT3 therapy course was longer (10–14 days) than the short course (5–7 days) of MALG prescribed. Differences in outcome could possibly be related to differences in the duration of treatment rather than inherent differences in the antilymphocyte preparations. Studies in the renal transplant population also suggest that the duration of treatment is an important variable [3, 9]. The courses of RATG and OKT3 prescribed at our institution are of approximately the same duration. It is likely, therefore, that differences in outcome observed in the patient groups that underwent transplantation at our institution relate to inherent differences in the antilymphocyte preparations.

Our study has various drawbacks. It suffers from the inherent disadvantages of a retrospective analysis. Moreover, patients were not strictly randomized into treatment groups between 1989 and 1992, but rather, according to the availability of locally produced RATG. Despite this there were significant benefits in survival and longer latencies to rejection in patients receiving RATG versus OKT3 in a large cohort of patients. These advantages have been maintained in recent years with our policy of favoring RATG and of reserving OKT3 for when adverse reactions to RATG develop. The data in this review emphasize the need for further investigation of the role of cytolytic induction therapy in heart-lung and lung transplantation as well as the optimal type and duration of therapy.

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