Effects of induction immunosuppression regimen on acute rejection, bronchiolitis obliterans, and survival after lung transplantation

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Objective: Effects of daclizumab and antithymocyte globulin induction on acute rejection, bronchiolitis obliterans syndrome, and survival after lung transplantation are unknown. We hypothesized that daclizumab results in less acute rejection and bronchiolitis obliterans and better survival than antithymocyte globulin.

Methods: Consecutive adult lung transplants ($n = 163$) at the University of Virginia from January 1998 to May 2006 were reviewed. Antithymocyte globulin induction was routinely performed before January 2002 (65 patients), after which all patients received daclizumab (98 patients). Estimates of cumulative event rate of acute rejection, bronchiolitis obliterans, and death were calculated by Kaplan–Meier method and between-group differences compared by log-rank test. Cox proportional hazards models were fitted to assess treatment effects adjusted for covariates.

Results: Groups were similar in demographics and preoperative and intraoperative risk factors. Maintenance immunosuppression changed during the study, and mycophenolate mofetil was more commonly given to patients receiving daclizumab. By Kaplan–Meier method, daclizumab was associated with significantly less acute rejection ($P = .002$), less bronchiolitis obliterans ($P = .02$), and improved overall survival ($P = .04$). Induction agent was highly associated with acute rejection ($P = .002$), bronchiolitis obliterans ($P = .02$), and mortality ($P = .05$); antimetabolite agent was associated only with acute rejection ($P = .01$). Adjusting for covariates, induction agent remained significantly predictive for acute rejection ($P = .02$) and bronchiolitis obliterans ($P = .05$), approaching significance for survival ($P = .07$).

Conclusion: Lung transplant recipients receiving daclizumab for induction had significantly less acute rejection and bronchiolitis obliterans than those receiving antithymocyte globulin, with possibly improved survival. Improvements in acute rejection may have been confounded by the use of mycophenolate mofetil.

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Lung transplantation for progressive end-stage pulmonary failure is the preferred treatment for appropriately selected surgical patients. Outcomes after lung transplantation are limited by acute rejection (AR) and particularly by chronic rejection, manifested as bronchiolitis obliterans syndrome (BOS).¹ According to data from the International Society for Heart and Lung Transplantation (ISHLT), AR affects more than 50% of recipients in the first year after transplantation.² Centers with aggressive screening programs have found pathologic evidence of AR in 85% of

Abbreviations and Acronyms

AR	= acute rejection
AT	= antithymocyte globulin
BOS	= bronchiolitis obliterans syndrome
CMV	= cytomegalovirus
HR	= hazard ratio
IL-2R	= interleukin 2 receptor
ISHLT	= International Society for Heart and Lung Transplantation
MMF	= mycophenolate mofetil
PTLD	= posttransplantation lymphoproliferative disorder

patients.³ It is well documented that AR is a significant risk factor for the development of BOS.⁴⁻⁵ BOS has been found in 45% of patients by 5 years after lung transplantation and is the most common cause (30%) of late death.² Induction agents have been shown to decrease the number of patients requiring treatment for AR. Routine use of a specific induction regimen has not been universally accepted, however, with approximately 50% of patients receiving no induction immunosuppression.² The two most common induction strategies are daclizumab (Zenapax), a monoclonal IgG antibody to interleukin 2 receptor (IL-2R), and antithymocyte globulin (AT), a polyclonal horse antibody to human thymus (primarily T lymphocytes). There remains considerable debate regarding which regimen is optimal for preventing AR.⁶⁻⁹ Moreover, no study has evaluated long-term outcomes of BOS and survival with different induction regimens. The purpose of this study was to examine the effects of daclizumab induction and AT induction on the incidences of AR and BOS and on survival.

Methods**Patient Population**

Data from patients undergoing lung transplantation are entered concurrently into the University of Virginia Lung Transplant Registry. Follow-up events are entered by our transplant coordinators as they occur. A retrospective review of 163 consecutive patients undergoing transplantation from January 1998 to September 2006 was performed, as approved by the University of Virginia Institutional Review Board (IRB 12006). All patients had complete data and follow-up. Standard single- or double-lung transplantation procedures were performed. Cardiopulmonary bypass was used selectively.

All transplant recipients received azathioprine (2.5 mg/kg) and methylprednisolone (1 g) before organ implantation. From 1998 to 2002, all patients (n = 65) underwent induction immunosuppression consisting of methylprednisolone (250 mg every 8 hours for three doses) and AT (15 mg/kg on day 1, 10 mg/kg on day 2, and 7.5 mg/kg on days 3–7; Pharmacia Corp, Kalamazoo, Mich). AT was stopped for hypersensitivity, leukopenia, or thrombocytopenia. Daily triple maintenance immunosuppression included cyclosporine (INN ciclosporin) or tacrolimus (serum trough goal of 10–15 ng/mL), azathioprine (2 mg/kg) or mycophenolate mofetil (MMF, 2 g),

and prednisone (20 mg). Beginning in January 2002, all patients (n = 98) received induction with methylprednisolone (as before) and daclizumab (Zenapax, 1 mg/kg on day of surgery, then every 2 weeks for a total of five doses; Hoffmann-LaRoche Inc, Nutley, NJ). Daily maintenance immunosuppression included cyclosporine or tacrolimus, MMF (2 g), and prednisone (20 mg). Patients received cytomegalovirus (CMV) prophylaxis during the study period with ganciclovir sodium (INN ganciclovir, 3 mg/kg twice daily) or valganciclovir hydrochloride (INN valganciclovir, Valcyte, 900 mg daily; Hoffmann-LaRoche) from day 7 through day 21. After completion of ganciclovir sodium, CMV prophylaxis was maintained with acyclovir (INN aciclovir, 800 mg four times daily). When the donor was positive for CMV and the recipient was negative for CMV, ganciclovir was continued until day 90 and CMV intravenous immune globulin (Cytogam; Genesis Bio-Pharmaceuticals, Hackensack, NJ) was administered (150 mg/kg on day 4 and at weeks 2, 4, 6, and 8, then 100 mg/kg at weeks 12 and 16).

The database contained donor age; recipient characteristics including age, sex, ethnicity, body mass index, diagnosis, and CMV status; operative events including single- versus double-lung transplantation, use of cardiopulmonary bypass, and graft ischemic time; and postoperative variables including oxygenation index, AR, BOS, and survival status. The variable of CMV mismatch was defined as differing donor and recipient CMV statuses. Graft ischemic time for double lung-transplantation was entered into the model as an average of the ischemic time for both lungs. Maintenance immunosuppression regimen was entered into the registry. Outcomes evaluated included AR, BOS, and mortality.

Definitions of AR and BOS

AR was defined by a panel of pulmonologists, thoracic surgeons, and pathologists and was agreed on by protocol; this definition did not change during the study period. Diagnosis was made according to either clinical or pathologic criteria. Clinical criteria included an acute change in symptoms, a new radiographic infiltrate, or a decrease in forced expiratory volume in 1 second of 20% from baseline not explained by infection or other cause. Lung biopsy was conducted if clinical criteria failed to diagnose AR. Pathologic diagnosis of rejection was defined by ISHLT grade A3 or higher histologic grade.¹⁰ Treatment included corticosteroids or augmentation of immunosuppression. BOS was determined by a decrease in pulmonary function testing greater than 20% from baseline (current forced expiratory volume in 1 second divided by two highest consecutive postoperative values). Follow-up data were used to derive comparisons between immunosuppression regimens with respect to the incidences of AR and BOS and to survival.

Statistical Analysis

Bivariate analyses between groups and categorical variables were done by either χ^2 test or Fisher exact test as appropriate. The 2-sample *t* test or Wilcoxon rank sum test was used to compare continuous variables. For comparing time to first episode of AR, time to first episode of BOS, and survival, the Kaplan–Meier method was used, and differences between groups were compared by log-rank test. Because median follow-up was 1.8 years in the daclizumab group, AR, BOS, and survival were compared with the χ^2 test at 2 years after transplantation. The Kaplan–Meier model did not account for repeated episodes of AR for a given patient or for

TABLE 1. Patient demographics, diagnosis, and intraoperative factors in patients receiving daclizumab or antithymocyte globulin induction

Variable	Daclizumab (n = 98)	Antithymocyte globulin (n = 65)	P value*
Donor age (y, median and range)	31.6 (9–63)	29.6 (14–61)	.38
Recipient factors			
Recipient age (y, median and range)	52.7 (21–68)	53.9 (25–69)	.52
Female (No.)	43 (44%)	35 (54%)	.21
African American (No.)	14 (14%)	6 (9%)	.33
Body mass index (kg/m ² , median and range)	24.4 (16–32)	25.2 (15–34)	.26
Cytomegalovirus mismatch (No.)	40 (40%)	24 (37%)	.62
Recipient diagnosis (No.)			.20
Chronic obstructive pulmonary disease	59 (60%)	38 (58%)	
Idiopathic pulmonary fibrosis	12 (12%)	15 (23%)	
Sarcoidosis	10 (10%)	6 (9%)	
Cystic fibrosis	13 (13.3%)	1 (1.5%)	
Bronchiectasis	1 (1.0%)	3 (4.6%)	
Lymphangioleiomyomatosis	1 (1.0%)	0 (0%)	
Primary pulmonary hypertension	1 (1.0%)	1 (1.5%)	
Eisenmenger syndrome	0 (0%)	1 (1.5%)	
Operative factors			
Oxygenation index (median and range)	5.6 (1.1–28.9)	4.6 (1.1–21.2)	.30
Graft ischemic time (min, median and range)	295.7 (110–549)	248 (80–528)	<.0001†
Need for CPB (No.)	18 (18.4%)	7 (10.8%)	.27
CPB time (min, median and range)	171.1 (54–323)	204.2 (117–246)	.27
Need for ECMO	3 (3.1%)	4 (6.2%)	.44
Double-lung transplant	26 (26.5%)	8 (12.3%)	.03†

CPB, Cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation. *P values were determined with *t* tests. †Significant difference.

progression of BOS. Cox proportional hazards models were fitted to investigate the effect of induction on AR, BOS, and survival, with adjustment for the covariates of donor age, recipient age, CMV mismatch, and diagnosis. All analyses were performed with SAS version 9.1.3 software (SAS Institute, Inc, Cary, NC).

Results

Sixty-five patients underwent AT induction (median follow-up 4.6 years), and 98 patients underwent daclizumab induction (median follow-up 1.8 years). Recipient characteristics, diagnoses, and operative factors are presented in Table 1. No differences in donor age, recipient age, ethnicity, body mass index, or CMV mismatch were identified. More than half of the transplant recipients undergoing AT induction were women, which was not significantly different from the daclizumab group. Diagnoses were similar between induction treatment groups. Graft ischemic times were significantly longer in the daclizumab group (mean $\pm$ SE 295 $\pm$ 8.1 minutes) than in the AT group (226.3 $\pm$ 10.6 minutes, *P* = .001). The number of patients undergoing double-lung transplantation significantly increased during the study period, from 12.3% (8/65) during the AT era to 26.5% (26/98) in the daclizumab era (*P* = .03). Importantly, among patients receiving AT, the median number of doses of the induction agent tolerated was four. Among the 65 patients in the AT

group, a total of 61 patients (94%) tolerated two doses of AT and 43 patients (66%) completed four doses of AT. In fact, only 2 patients (3%) were able to tolerate a complete 7-day course per our induction protocol. AT was discontinued because of severe hypersensitivity reactions, leukopenia, thrombocytopenia, or evidence of infection.

Initial maintenance immunosuppression in the AT group varied during this study period as a result of the introductions of MMF and tacrolimus (Table 2). In the AT group, 11 patients received cyclosporine, whereas 53 patients received tacrolimus. In this same group, 5 patients received MMF, and 58 patients were treated with azathioprine. The daclizumab

TABLE 2. Maintenance immunosuppression during the study period

Maintenance agent	1998-2002*	2002-2006†
Interleukin 2 inhibitor		
Cyclosporine	11	5
Tacrolimus	53	93
Antimetabolite		
Azathioprine	58	5
Mycophenolate mofetil	5	93

*Induction agent in period from 1998 to 2002 was antithymocyte globulin.

†Induction agent in period from 2002 to 2006 was daclizumab.

Figure 1. A, Kaplan–Meier probability curve comparing incidences of acute rejection after daclizumab and antithymocyte globulin (ATGAM) induction. B, Kaplan–Meier probability curve comparing incidences of BOS after daclizumab and antithymocyte globulin (ATGAM) induction. C, Kaplan–Meier survival curves for lung transplantation after daclizumab and antithymocyte globulin (ATGAM) induction.

group received mainly tacrolimus (93 patients) rather than cyclosporine (5 patients) and MMF (93 patients) rather than azathioprine (5 patients).

According to the Kaplan–Meier method, AR occurred less frequently among patients receiving daclizumab than among those undergoing AT induction ($P = .002$; Figure 1, A). AR tended to occur in the first 3 to 6 months after transplantation, irrespective of induction regimen. Beyond 6 months, the Kaplan–Meier estimator curves are parallel, regardless of induction regimen. At 2 years after transplantation, patients receiving daclizumab had less AR (9%, 9/98) than did patients receiving AT (28%, 18/65, $P = .002$). The time to the first

episode of BOS was significantly shorter among patients undergoing AT induction than among those undergoing daclizumab induction ($P = .02$; Figure 1, B). In the group receiving daclizumab, BOS rarely occurred until 2 years after transplantation, whereas AT induction patients had BOS develop as early as 1 year after transplantation. The two curves have different slopes, suggesting less BOS with time after daclizumab induction. At 2 years after transplantation, BOS was less common among patients who received daclizumab (6.4%, 6/96) than among those who received AT (23%, 14/60, $P = .002$). Furthermore, daclizumab induction demonstrated improved survival relative to AT

TABLE 3. Bivariate (univariate) analysis of acute rejection, bronchiolitis obliterans syndrome, and mortality

Variable	P values*		
	Acute rejection	Bronchiolitis obliterans	Death
Donor age	.67	.98	.89
Recipient age	.28	.61	.71
Induction agent	.002†	.02†	.05†
Maintenance immunosuppression			
Mycophenolate mofetil vs azathioprine	.01†	.09	.07
Tacrolimus vs cyclosporine	.40	.09	.53
Double-lung transplant	.10	.86	.77
Ethnicity	.76	.12	.65
Sex	.06	.90	.97
Body mass index	.27	.42	.81
Diagnosis	.40	.84	.60
Cytomegalovirus mismatch	.18	.89	>.99

*P values from Cox proportional hazards models. †Significant difference.

induction ($P = .04$; Figure 1, C). At 2-year follow-up, survival in the daclizumab group was 94%, compared with 83% survival in the AT group ($P = .03$).

Bivariate analyses were performed to identify variables influencing the three outcomes (Table 3). AR was strongly associated with induction regimen ($P = .002$) and antimetabolite maintenance drug ($P = .01$). Calcineurin inhibitor was not significantly associated with AR. BOS was associated with induction ($P = .02$) but not with other variables, including maintenance immunosuppression. Mortality was significantly associated only with induction ($P = .05$) and not with recipient or donor age, body mass index, diagnosis, CMV mismatch, or maintenance immunosuppression.

A Cox proportional hazards model was fitted to adjust for other covariates. Induction agent was the only variable associated with all three outcomes. Antimetabolite was associated only with AR. Because of a high correlation between antimetabolite agent and induction agent (Table 2), both variables could not be added to the model; this would have resulted in a statistically invalid model. In an attempt to distinguish the confounding effects of antimetabolite maintenance immunosuppression on AR, analysis of maintenance immunosuppression within each induction group was performed. Among patients who received AT induction, AR developed in 20% of patients receiving MMF (1/5) and 31% of patients receiving azathioprine (18/40, $P = .60$). Among patients receiving daclizumab induction, AR developed in 9% of patients receiving MMF immunosuppression (9/93) and in 0% of those receiving azathioprine (0/5, $P = .46$). Other clinically significant variables of induction regimen, donor age, recipient age, CMV mismatch, and diagnosis were included in the model (Table 4). Type of induction reg-

TABLE 4. Multivariate analyses (Cox proportional hazards models) for acute rejection, bronchiolitis obliterans syndrome, and mortality

Variable	Hazard ratio	95% Confidence interval	P value
Acute rejection			
Induction (antithymocyte globulin vs daclizumab)	2.71	1.15–6.39	.02*
Donor age (per y)	1.00	0.98–1.04	.73
Recipient age (per y)	0.94	0.90–0.99	.03*
CMV mismatch (vs CMV match)	1.78	0.79–4.03	.17
Diagnosis (vs COPD)			
Idiopathic pulmonary fibrosis	0.75	0.25–2.27	.60
Sarcoid	0.19	0.02–1.59	.12
Other†	0.14	0.02–0.91	.04*
Bronchiolitis obliterans syndrome			
Induction (antithymocyte globulin vs daclizumab)	2.12	0.99–4.49	.05*
Donor age (per y)	1.00	0.98–1.02	.95
Recipient age (per y)	0.97	0.94–1.01	.18
CMV mismatch (vs CMV match)	1.64	0.81–3.32	.17
Diagnosis (vs COPD)			
Idiopathic pulmonary fibrosis	1.08	0.48–2.44	.86
Sarcoid	1.85	0.55–6.20	.31
Other†	0.42	0.12–1.50	.18
Death			
Induction (antithymocyte globulin vs daclizumab)	2.31	0.92–5.78	.07
Donor age (per y)	1.00	0.97–1.03	.98
Recipient age (per y)	1.00	0.96–1.04	.89
CMV mismatch (vs CMV match)	1.43	0.68–2.98	.35
Diagnosis (vs COPD)			
Idiopathic pulmonary fibrosis	1.48	0.65–3.38	.35
Sarcoid	2.78	0.86–8.98	.08
Other†	1.03	0.29–3.67	.99

CMV, Cytomegalovirus; COPD, chronic obstructive pulmonary disease. *Significant difference. †Other diagnoses were cystic fibrosis, bronchiectasis, primary pulmonary hypertension, Eisenmenger syndrome, and lymphangioleiomyomatosis.

imen was significantly associated with AR, with a hazard ratio (HR) of 2.71 ($P = .02$). Interestingly, younger recipient age was weakly but significantly associated with AR (HR 0.94, $P = .03$).

Specific induction regimen was significantly associated with the onset of BOS (HR 2.12, $P = .05$), with AT being associated with the onset of BOS. Furthermore, AT induction approached a significant correlation with mortality (HR 2.31, $P = .07$). No other variable, including diagnosis, was

independently associated with mortality after adjustment for other covariates.

From our analyses, AR was correlated with BOS, and BOS was correlated with mortality. During the study period, 46% of patients with AR (13/28) had BOS develop, compared with 26% of patients who did not have an episode of AR (35/135) who had BOS develop ($P = .04$). Similarly, 42% of patients with BOS died during the study period, compared with 18% of patients who died without any antecedent BOS (21/115, $P = .002$).

The incidence of malignancy and posttransplantation lymphoproliferative disorder (PTLD) was not different between the two induction groups. Five patients in the AT group (7.7%) and 3 patients in the daclizumab group (3.1%) had malignancy develop during follow-up ($P = .26$). Only 1 patient in the daclizumab group and no patients in the AT group had PTLD develop.

Discussion

This study examined the effects of daclizumab and AT induction on the incidence of AR and BOS and on survival in 163 consecutive lung transplant recipients at a single institution. January 2002 marked the point at which the routine induction agent changed from AT to daclizumab for all patients at our institution. Despite relatively similar demographic data in the patient groups, patients receiving daclizumab induction demonstrated less AR and less BOS, with a trend toward improved survival relative to AT induction. Only 3% of patients were able to tolerate the full AT induction, whereas all patients tolerated induction with daclizumab. With so few patients in the AT group completing induction, patients were stratified by an intention-to-treat analysis by induction agent, rather than by a dichotomous variable of completion of induction versus incomplete induction.

The rationale for induction therapy for organ transplantation is to suppress the initial host immune response to the allograft. This strategy has been shown to decrease the incidence of AR in kidney and combined kidney–pancreas transplantation.^{11–12} In lung transplantation, longitudinal studies indicate that AR primarily occurs within 4 months after transplantation and decreases with time.¹³ Despite the rationale for induction therapy, according to ISHLT data, more than 50% of lung transplant recipients do not receive any induction agent.²

Specifically, IL-2R antagonists have been shown to affect the development of AR. In kidney as well as heart transplant recipients, induction immunosuppression with daclizumab, a potent IL-2R monoclonal antibody, has been associated with a decrease in the number of episodes of AR.^{14–15} The efficacy of daclizumab as an induction agent in preventing AR after lung transplant has been studied.^{6–9} Garrity and colleagues⁶ demonstrated that the incidence of grade 2 AR significantly decreased from 48% without induction to 18% with daclizumab during the first 6 months after transplantation.

Few studies have compared daclizumab with AT as induction immunosuppression for lung transplantation. In a prospective trial, Brock and associates⁷ demonstrated no differences in AR, BOS, or survival among three induction regimens (OKT3, AT, and daclizumab). Despite a relatively small sample size in each group (total of 87 patients divided into three groups), however, patients receiving daclizumab had significantly fewer infections than did those receiving the other two induction agents. Burton and colleagues⁸ analyzed over more than lung transplant recipients and documented less AR with AT induction than with daclizumab. In that study, 100% of patients receiving daclizumab induction had AR by 2 years after transplantation, a rate notably higher than in any other study, and outcomes of BOS and mortality were not reported. In a recent report of 25 patients, daclizumab was associated with significantly improved freedom from AR relative to AT.⁹

Although the effects of induction therapy on AR have been documented, outcomes of BOS and survival have not been well described. Only one previous study attempted to find any differences between daclizumab and AT induction with respect to BOS or survival. This small study (25 patients) did not find significant differences. Larger studies comparing the two induction agents have not evaluated BOS or survival. AR is the most important risk factor for the development of BOS.^{4,5} BOS is the most common cause of death after lung transplantation.² In our report, AR was significantly associated with the development of BOS, and BOS in turn was significantly associated with mortality during the study period. Our investigation supports the concept that AR, BOS, and survival are related outcomes.

Despite conflicting data regarding daclizumab versus AT induction, the ISHLT Registry has noted increasing use of IL-2R antibody induction rather than AT.² In fact, daclizumab induction is used for more than 30% of lung transplant recipients, whereas AT induction has declined to approximately 10%.² There are several explanations for the increased use of daclizumab. First, AT is not well tolerated, as seen in our study, with a minority of patients in the AT group completing our induction protocol because of significant adverse effects. Second, patients receiving AT induction demonstrate higher infection rates than are seen with daclizumab induction.⁷ In a study of heart transplant recipients, bacterial infections were three times more likely after AT induction than after daclizumab induction.¹⁶ Brock and associates⁷ reported that viral infections were three times more common after AT induction than after daclizumab induction. Finally, the risk profile of daclizumab is low, and the agent appears to be well tolerated. In our study, no patient required the discontinuation of daclizumab because of an adverse effect.

According to bivariate analysis, only induction agent was a significant predictor for all three outcomes. Importantly, antimetabolite maintenance agent was associated with the outcome of AR but not with BOS or mortality. Antimetabolite

maintenance agent would ideally have been added to the multivariate model, because it is a confounding variable. Because of the strong correlation between the use of MMF and daclizumab, however, the two variables (induction and maintenance immunosuppression) could not be put into the model together, as this would render the model statistically invalid. Analysis of antimetabolite agent within each induction group did not show any correlation with AR. This subgroup analysis was limited by type II error because of the small sample sizes of 5 patients in maintenance immunosuppression groups. It is possible that with larger sample sizes, maintenance immunosuppression might correlate with all three outcomes. Patients undergoing double-lung transplantation have been shown to have a survival advantage relative to patients undergoing single-lung transplantation.² Even though there were significantly more patients undergoing bilateral lung transplantation in the daclizumab group in our study, there was no correlation between double-lung transplantation and the three outcomes according to bivariate analysis. Other clinically important variables were therefore selected for the multivariate model. Data from ISHLT has demonstrated higher mortality after lung transplantation to be associated with donor age, recipient age, CMV mismatch, and diagnosis.²

Our study has several limitations. First, it is a retrospective, single-institution study with inherent biases. Our two patient populations were similar, however, with respect to baseline characteristics and intraoperative data (Table 1). Second, there were notable differences in maintenance immunosuppression during our two study periods. There are conflicting data regarding the effects of specific maintenance regimens on outcomes. In a recent multicenter randomized trial, azathioprine and MMF did not differ with respect to the development of AR or BOS or to survival at 3 years.¹⁷ Previous studies have compared tacrolimus and cyclosporine in the treatment of AR and BOS. A retrospective review demonstrated that tacrolimus was superior to cyclosporine for patients with AR or BOS.¹⁸ In contrast, a prospective, randomized study demonstrated no differences in associated BOS or survival between tacrolimus and cyclosporine.¹⁹ Several multicollinear variables were evaluated in our study. Daclizumab was used most often in conjunction with MMF during a more mature era of our lung transplant program. These variables are difficult to separate because of their collinearity and also the limited sample size. It is likely that some of the effects seen on these three outcomes are due to concomitant effects daclizumab and MMF. Third, although we did not find any differences in the selection, intraoperative management, or postoperative care of these transplant recipients with time, our lung transplant program has matured, with greater experience of our lung transplant surgeons and pulmonologists and greater use of bilateral lung transplantation. Collectively, the improved evolution of our program may have contributed to our improved outcomes in patients who received daclizumab. The ISHLT Registry has reported

an improvement in survival in recent transplant recipients relative to earlier eras.² As such, the improved survival in the later group with the use of daclizumab induction may also be related to improvements in processes of care. Fourth, our median follow-up of 1.8 years in the daclizumab group was short. With longer follow-up, it is possible that the benefits seen after daclizumab induction may be lost. Finally, the seven daily AT doses used in our study differ from previous reports. Burton and colleagues⁸ administered AT at 12.5 mg/(kg · d) for three doses, whereas the protocol used by Brock and associates⁷ included a 7-day course of AT starting at 15 mg/(kg · d) and adjusted daily. Neither report documented the number of patients who received all intended doses. Differences in our AT protocol relative to other studies may in part explain our outcomes.

PTLD has been linked to the use of induction agents after renal transplantation.²⁰ In one study, an IL-2R inhibitor as an induction agent was not associated with any increase in PTLD relative to no induction, whereas use of AT induction was associated with a 55% increase in PTLD.²⁰ Because of the relatively low incidence of any type of malignancy in our study, we did not document differences in malignancy after either induction agent.

In conclusion, AR and BOS were improved in patients receiving daclizumab induction immunosuppression relative to AT. In addition, there was a trend toward improved survival among patients receiving daclizumab. Poor tolerance to AT resulted in fewer patients completing the induction protocol. Differences in maintenance immunosuppression during the two different periods, as well as improvements in the evolution of care of our maturing lung transplant program, may also explain these outcomes. This study supports the need for prospective, randomized trials comparing induction agents in lung transplantation.

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Discussion

Dr Yoshiya Toyoda (Pittsburgh, Pa). What do you think is the mechanism of the difference in outcome between daclizumab and AT, because previously we have shown there is no difference in AR and survival between daclizumab and AT, and alemtuzumab induction is much better in terms of AR. Are there any differences

in, for example, pulmonary protection or preservation protocols for infection, prophylaxis, or ventilatory management?

Dr Ailawadi. Those are good questions. The question is basically to try to elucidate why we saw these differences between the AT group and the daclizumab group. Primarily, what we saw with our patients receiving AT was that they got very sick, and few patients were able to tolerate the full course of AT induction. Patients receiving daclizumab were all able to tolerate the full treatment courses, as long as they survived, as most of them did.

As to why AR, BOS, and survival would all have similar outcomes dependent on induction, what we see is that of all patients who had AR, 46% went on to have BOS, and approximately 42% of patients that had BOS died during the study period. So these three outcomes are clearly linked. Our hope is that if we can prevent the first insult, AR, we may be able to interfere with later outcomes.

Dr Toyoda. Have you checked T-cell or B-cell counts to, for example, 6 months? With alemtuzumab induction, those are significantly less. That can explain this AR.

Dr Ailawadi. We do not routinely check T or B cell counts.

Dr Toyoda. Then you changed your lung preservation or protection protocol?

Dr Ailawadi. There were no differences. We used the same preservation agent during the study period.

Dr Mark J. Krasna (Towson, Md). Just to follow up that last question, during this long period, were there any other changes in technique? Obviously, you talked about the maturation of the program. I assume that if you looked at the number of cases per year, it probably increased in the later years. Were there any changes in technique that might have had significance?

Dr Ailawadi. We really looked hard for any differences, and we did not find anything concrete that was different. Our volumes increased slightly during the study period, ranging from 16 transplants per year in the AT era to 20 transplants per year in the daclizumab era.

Dr Bansi Koul (Lund, Sweden). I was wondering about these two series conducted over time. How about patients with, say, HLA antibodies? How are you managing those patients, or did you exclude those from this study?

Dr Ailawadi. We routinely used these induction agents in all our patients. So we did not exclude any patients because of HLA antibodies.

Dr Koul. So you are confident in using daclizumab for patients who have a high percentage of antibodies in the blood, without any monitoring for them in the early postoperative period?

Dr Ailawadi. We monitor them for clinical outcomes. We used daclizumab for all patients, even those with high antibody levels.

Shu S. Lin (Durham, NC). I congratulate you for presenting such a clear study. I do have one question; during your analysis did you find any difference in the number of biopsies obtained in the two eras?

Dr Ailawadi. That is a good question. We have not looked at that, and it would be interesting to know the number of patients who underwent diagnosis by various criteria, whether pathologic or clinical criteria.

Dr Krasna. Just one other question perhaps you could clarify for us. You obviously have some ideas about why you see the difference in AR in those patients with chronic obstructive pulmonary disease, something that you have never heard before, or why this is only the

second time we have heard a relationship with sarcoid and BOS. Do you want to give us a supposition on your part or what your impression is?

Dr Ailawadi. As for the chronic obstructive pulmonary disease, I don't have a good explanation. With regard to the sarcoid, it obviously is a different disease process, and there is probably some autoimmune process going on. The study to which I referred is actually out

of Pittsburgh in 1999. It studied a very small group of patients and, as a matter of fact, didn't reach statistical significance, but patients who underwent transplantation for sarcoid had an incidence of BOS of 50%, significantly greater than their experience with other diagnoses.

Dr Gus J. Vlahakes (*Boston, Ma*). In what model is the daclizumab produced? How is it made? Is it made in a murine model?

Dr Ailawadi. It is a recombinant antibody.

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