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FIVE-YEAR OUTCOMES WITH ALEMTUZUMAB INDUCTION AFTER LUNG TRANSPLANTATION

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Abstract

Background—Induction therapy with alemtuzumab, followed by lower than conventional intensity posttransplant immunosuppression (e.g., tacrolimus monotherapy), has been associated with reduced morbidity and mortality in abdominal and heart transplantation. We examined 5-year outcomes in lung recipients receiving alemtuzumab in conjunction with reduced intensity posttransplant immunosuppression (early lower dose tacrolimus; lower dose steroids, with or without mycophenolate mofetil), compared to lung recipients receiving other induction agents or no induction in association with posttransplant immunosuppression.

Methods—A retrospective analysis was performed utilizing prospectively collected data from a single-site clinical database on 336 lung recipients (aged ≥18) transplanted between 1998 and 2005, classified by induction type: alemtuzumab (n=127), Thymoglobulin (n=43), daclizumab (n=73), none (n=93). Survival analyses examined patient and graft survival, and freedom from

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acute cellular rejection (ACR), lymphocytic bronchiolitis, obliterative bronchiolitis (OB), bronchiolitis obliterans syndrome (BOS), and post-transplant lymphoproliferative disorder (PTLD).

Results—Five-year patient and graft survival differed by group ($p=.046$, $p=.038$, respectively). Alemtuzumab patient/graft survival rates were 59%/59%. Survival rates were 60%/44% for Thymoglobulin, 47%/46% for no-induction, and 44%/41% for daclizumab. Freedom from ACR, lymphocytic bronchiolitis, OB, and BOS differed by group (all p 's $<.008$); alemtuzumab recipients showed greater 5-year freedom from each outcome (30%/82%/86%/54%) than Thymoglobulin (20%/54%/62%/27%), daclizumab (19%/55%/70%/43%) and no-induction groups (18%/68%/69%/46%). The groups did not differ in PTLD rates ($p=.864$, $\geq 94\%$ free of PTLD at 5 years). Effects were unchanged after controlling for potential covariates.

Conclusions—Alemtuzumab induction may be associated with improved outcomes in lung transplantation. Randomized controlled trials are needed to establish any effects of this agent.

INTRODUCTION

Survival after lung transplantation remains relatively poor, with 5-year rates of 52%–54%.^{1–3} Five-year survival rates are 73%–91% for other types of solid organ transplantation.⁴ Chronic rejection, presenting histologically as bronchiolitis obliterans (OB) or clinically as bronchiolitis obliterans syndrome (BOS),^{5–7} is a major contributor to posttransplant mortality.¹ Furthermore, acute cellular rejection and lymphocytic bronchiolitis—both sources of morbidity after lung transplantation—are risk factors for chronic rejection.^{5–9–11}

The traditional “triple drug” immunosuppression regimen (consisting of a calcineurin inhibitor, an antimetabolite, and high corticosteroid doses), used with or without a short course of an antilymphoid antibody (induction), has had limited success in preventing acute rejection after lung transplantation.^{12–13} Moreover, neither the preventive nor therapeutic immunosuppressive strategies typically employed after lung transplantation have been effective against chronic rejection,¹³ and complications from drug-specific toxicities are common.¹³ Induction agents may predispose transplant recipients to develop posttransplant lymphoproliferative disorder (PTLD), which further contributes to mortality.¹⁴

Alemtuzumab (Campath-1H; Berlex Laboratories, Montville, NJ), used as an induction agent, in combination with reduced calcineurin inhibitor and antimetabolite exposure, and low steroid maintenance therapy, shows promise for addressing these issues in lung recipients. It is a monoclonal anti-CD52 antibody, and results in renal transplantation indicate that alemtuzumab induction allows for minimal posttransplant immunosuppression regimen without increased risks of acute rejection or PTLD.^{15–22} There may also be benefits in liver,^{23–24} intestinal,^{25–26} and heart transplantation.^{27–28}

In lung transplantation, McCurry et al.²⁹ found alemtuzumab induction followed by tacrolimus monotherapy or tacrolimus with low-dose steroids to result in fewer, less severe acute rejection episodes and decreased rates of cytomegalovirus (CMV) infection, compared to induction with Thymoglobulin (rabbit antithymocyte globulin; SangStat, Fremont CA) followed by tacrolimus with low-dose steroids, or induction with daclizumab (Zenepax) followed by standard triple therapy. However, van Loenhout et al.³⁰ found no difference in survival or acute rejection among patients treated with alemtuzumab induction and low-intensity maintenance immunosuppression relative to a no-induction control group. Both studies relied on small samples of ≤ 20 patients receiving alemtuzumab induction, and considered outcomes during only the first year posttransplant. The longer-term morbidity and mortality rates following alemtuzumab induction in lung transplantation remain unknown.

In the present study, we examined whether lung recipients receiving an alemtuzumab induction-based regimen with early reduced-intensity maintenance immunosuppression showed lower morbidity and mortality risks across the first five years posttransplant relative to patients receiving immunosuppressive regimens with other induction agents or no induction therapy.

METHODS

Study design and subjects

This was a retrospective review of electronic medical records of all adults (aged ≥ 18) receiving their first single-, bilateral-, or heart-lung transplant between September 1998 and September 2005. All were transplanted at the University of Pittsburgh Medical Center (UPMC). The study design was a retrospective sequential cohort study without internal controls, i.e., subjects were classified into four study groups according to the induction therapy protocol in clinical use at the time of their transplant: alemtuzumab, Thymoglobulin, daclizumab, or no induction (see Table 1).

The University of Pittsburgh Institutional Review Board (IRB) approved the present study. It utilized patient data that had been prospectively entered into the UPMC Cardiothoracic Transplantation Program's electronic clinical records management database, the Transplant Patient Management System (TPMS). The data were supplemented by review of patients' UPMC medical records. Patients' receipt of induction therapy as part of their immunosuppression regimen had been deemed by the IRB not to be a research activity³¹ but instead to be within the purview of the Presbyterian University Hospital Innovative Practices Committee and the Pharmacy and Therapeutics Committee, both of which approved it. Patients thus provided standard informed consent for transplantation and all clinical care.

Immunosuppressive Protocol and Clinical Management

Induction drug infusions began before allograft reperfusion. Patients given alemtuzumab received 30 mg infused steadily over 2 hours. Patients given Thymoglobulin received 3–6 mg/kg, begun slowly with rate escalation every 30 minutes. Patients given daclizumab received five doses (1 mg/kg on day 0, posttransplant day 7, and at 2-week intervals thereafter; this dosing schedule was adopted from that in use at the time with heart recipients at our center). All patients received 250 mg of methylprednisolone immediately before reperfusion, and tacrolimus beginning on postoperative day 1. The maintenance immunosuppression protocol for each study group is shown in Table 1.

Patients followed a standard posttransplant care regimen, including surveillance bronchoscopy with transbronchial biopsy and bronchoalveolar lavage, spirometry, physical examination, and blood work. The surveillance protocol included biopsies every 3–4 months during the first two years for patients transplanted before 2002. Thereafter, it was increased to every 2–3 months during the first year and every 3–4 months during the second year, with the intent of detecting asymptomatic graft rejection. Beyond two years posttransplant, all patients received follow-up every 4–6 months, with bronchoscopy if clinically indicated (based on observed symptoms such as fever, cough, shortness of breath, decline in lung function). Patients engaged in home monitoring of health status (e.g., spirometry).

Diagnosis and Treatment of Rejection

Acute cellular rejection (ACR) and airway inflammation (lymphocytic bronchiolitis, LB) were diagnosed by histologic examination of transbronchial or open lung biopsy specimens according to ISHLT criteria in use at the time the biopsies were graded.^{6,32} Specimens were

reviewed at weekly conferences. ACR and LB were treated with corticosteroids (10-day oral prednisone taper or up to 3 doses of 1000 mg of methylprednisolone) and occasionally with augmentation or addition of baseline agents, particularly when they were higher grade. In the alemtuzumab and Thymoglobulin groups, grade A2 ACR often was not treated in the absence of deterioration of allograft dysfunction unless there were histopathologic findings of tissue injury. All grade A2 ACR episodes in the daclizumab and no-induction groups were treated. Grade B2R6 (high grade,32 B3 and B4) was treated in all groups.

Infection Prophylaxis

For the alemtuzumab and Thymoglobulin groups, prophylaxis against CMV was 450–900 mg/d valganciclovir for 6 months. Prophylaxis against fungus and yeast was intravenous 6 mg/kg voriconazole every 12 hours for 2 weeks, followed by 200 mg twice daily for 4 months. The daclizumab group received the same dose of valganciclovir, but fungal and yeast prophylaxis consisted of 3 months of fluconazole. The no-induction group received intravenous 5 mg/kg ganciclovir every 12 hours for 2 weeks, followed by 5 mg/kg daily for 3 months, and fluconazole. All patients received one trimethoprim/sulfamethoxazole single strength tablet thrice weekly for *Pneumocystis carinii* prophylaxis.

Outcomes

Medical records data were retrieved for each patient for a maximum of five years posttransplant, with censoring at time of death. At least two investigators assigned outcomes and reached consensus in the case of disagreement.

Seven outcomes were examined. They included patient survival and graft survival (defined as time to graft loss, either death or retransplantation). ACR was defined as grade $\geq$ A2, and LB was defined as grade B2R (high grade,32 $\geq$ B3), assigned according to standard criteria in use at the time the biopsies were graded.^{6,32} The date of the first biopsy indicating ACR, and the first indicating LB, was recorded. Chronic graft rejection was considered with two separate outcomes: histological evidence of OB (according to ISHLT criteria,^{6,32}) and the presence of its clinical surrogate, BOS at grade $\geq$ 1 (by ISHLT criteria),⁹ For each, the earliest date at which the outcome was present was recorded. PTLD was diagnosed by histopathologic examination of biopsy specimens. The date of diagnosis was recorded.

Statistical Analysis

Descriptive data on study groups' demographic and clinical characteristics were examined using chisquared tests (for proportions) and F tests (for means). Differences in time to each outcome were examined using Kaplan-Meier analysis in order to account for any data censoring (i.e., censoring due to patient death when considering other outcomes). For outcomes with significant between-group differences, Cox regression analyses³³ were performed to determine whether the differences remained after controlling for potentially important covariates (e.g., patient age).

RESULTS

Study Group Characteristics

Study groups were similar on most characteristics at transplant (Table 2). However, the Thymoglobulin group averaged 5–6 years younger than other groups. The Thymoglobulin and alemtuzumab groups included more bilateral lung transplants (and longer ischemia times) than the remaining two groups. This may reflect the fact that bilateral lung transplantation has become more prevalent over time.¹ Thymoglobulin patients had longer length of hospital stay at the transplant admission and more readmissions during the first year posttransplant than other patient groups.

Patient survival

Five-year patient survival rates differed significantly across the study groups (Breslow $\chi^2=8.01$, $df=3$, $p=.046$; see Figure 1a for the groups' survival curves). (See Appendix for a listing of the specific survival and other outcome rates generated from the Kaplan-Meier analyses.) Survival was 60% in the Thymoglobulin group and 59% in the alemtuzumab group at five years, with lower rates in the daclizumab and no-induction groups (44% and 47%). Additional pairwise comparisons indicated that the alemtuzumab group had significantly higher survival than the no-induction ($p=.011$) and daclizumab groups ($p=.045$). There were no other significant pairwise comparisons.

There were 159 deaths. The most prominent causes were infection and graft failure (Table 3). Although the study groups did not differ in distribution of deaths by infection, pulmonary factors or malignancy, the groups differed significantly in deaths due to graft failure, with the alemtuzumab group showing the lowest percentage of deaths from this cause.

Graft survival

Five-year graft survival rates differed significantly across the groups ($p=.038$; Figure 1b). Alemtuzumab recipients' graft survival rate at five years was 59%, followed by the no-induction (46%), Thymoglobulin (44%) and daclizumab groups (41%). The alemtuzumab group differed significantly from the no-induction ($p=.009$) and daclizumab groups ($p=.028$), and differed marginally from the Thymoglobulin group ($p=.059$). There were no other significant pairwise differences.

There were 169 recipients with graft loss, of whom 14 received retransplantation. Thymoglobulin patients with graft loss were significantly more likely to receive retransplantation (33.3%; $n=8$ of 24 cases: 8 due to OB, 1 for primary graft failure) than daclizumab patients (4.7%, $n=2$ of 43 cases: 1 OB, 1 primary graft failure), no-induction patients (2.0%, $n=1$ of 50 cases, OB), and alemtuzumab patients (3.8%, $n=2$ of 52 cases: 1 OB, 1 primary graft failure) (Fisher's exact test, $p<.001$).

Acute cellular rejection

Freedom from ACR differed significantly across the groups ($p<.001$; Figure 2a). Pairwise comparisons indicated that the alemtuzumab group had a significantly greater freedom from ACR by five years posttransplant (29%) than each of the other groups ($p<.001$). There were no significant pairwise differences between the Thymoglobulin (20%), daclizumab (19%), and no-induction groups (18%).

Lymphocytic bronchiolitis

Freedom from LB differed significantly across the groups ($p<.001$; Figure 2b). Pairwise comparisons indicated the following significant differences: the alemtuzumab group had a greater freedom from LB (78%) than the daclizumab (55%) and Thymoglobulin (54%) groups ($p<.001$). The no-induction group also had greater freedom from LB (70%) than the daclizumab ($p=.043$) and Thymoglobulin groups ($p=.020$).

Chronic rejection

Freedom from OB through five years posttransplantation differed significantly across the groups ($p=.003$; Figure 3a). The alemtuzumab group maintained the highest rate of freedom from OB (86%), followed by the daclizumab (70%), no-induction (69%), and Thymoglobulin groups (62%). The alemtuzumab group had significantly greater freedom from OB than each of these three groups (p 's of .004, .002, and $<.001$, respectively). There were no other significant pairwise differences.

The study groups also differed in freedom from BOS ($p=.008$; Figure 3b); freedom from this outcome at five years was 54%, 46%, 43%, and 27% for the alemtuzumab, no-induction, daclizumab, and Thymoglobulin groups, respectively. The pairwise comparison of rates between the alemtuzumab and Thymoglobulin group was significant ($p<.001$); the alemtuzumab and daclizumab groups differed marginally ($p=.053$). There were no other significant pairwise differences.

PTLD

Eleven patients (3.3%) developed PTLD. There was no significant difference across the study groups in PTLD incidence ($p=.864$; Figure 4). All groups showed high rates ($\geq 94\%$) of freedom from PTLD. Although the number of individuals with Epstein Barr virus (EBV) mismatch was small ($n=13$), we examined descriptively whether PTLD was more common in some study groups than others. PTLD developed in one of the five patients in the no-induction group who had an EBV mismatch (at 1.0 years posttransplant), one of the two daclizumab patients (at 0.3 years posttransplant), one of the three Thymoglobulin patients (at 0.2 years posttransplant) and three of the three alemtuzumab patients (at 0.5, 0.9, and 2.4 years posttransplant).

Multivariate analyses

For each of the six outcomes for which we observed significant study group differences, we utilized Cox regression analysis to determine whether those differences remained after controlling for covariates at time of transplant that were significantly correlated with group membership. Thus, we regressed each outcome on study group, patient age, type of transplant, and ischemia time. We also included indication for transplant as a covariate. After the covariates were controlled, statistically significant study group differences remained for each outcome: patient survival ($p=.017$), graft survival ($p=.008$), ACR ($p=.001$), LB ($p=.002$), OB ($p=.041$) and BOS ($p=.027$). Among the covariates, only type of transplant was significantly ($p<.05$) associated with outcomes, with bilateral lung recipients showing better patient and graft survival and lower ACR risk ($p<.050$).

DISCUSSION

The most recent ISHLT Registry data¹ indicate that 62% of adult lung recipients worldwide in the last several years have received induction therapy. Of these, 14% received alemtuzumab; this percentage has more than doubled since 2004.¹ We have continued its use in our program, given favorable results in abdominal transplantation,^{15–26} and early findings in cardiothoracic transplantation.^{27–30}

However, there are few empirical data on long-term outcomes with this therapy in lung recipients. To our knowledge, the present report describes the largest study with the longest follow-up to date of lung recipients receiving alemtuzumab induction. Our results suggest that, compared to other treatment regimens posttransplantation, an alemtuzumab induction-based immunosuppression regimen was associated with improved survival outcomes, particularly graft survival, decreased incidences of ACR, LB, and reduced risk of chronic rejection. We observed no statistically or clinically significant difference in PTLD risk, although the total number of events was small.

The significantly greater freedom from acute cellular rejection in alemtuzumab recipients extends earlier work by McCurry et al.²⁹ examining the early months posttransplant. The findings are all the more striking since the increased rate of surveillance biopsies during the first year posttransplant in recent years at our center might have been expected to identify more incident cases of ACR and OB in alemtuzumab patients relative to remaining patients

who were transplanted previously. McCurry et al.²⁹ noted that the prolonged depletion of T cells by alemtuzumab was associated with lower acute rejection rates, and therefore a decreased incidence of acute rejection in our sample would be expected. We also observed that alemtuzumab patients had relatively greater freedom from LB. Both ACR and LB are risk factors for chronic rejection,^{5,8,9,34} and this may account for our findings of reduced risk for and delayed onset of both OB and BOS in alemtuzumab recipients, relative to other patient groups. However, the causal nature of these risk factor effects remains unclear. Thus, for example, ACR may be only a marker of general alloreactivity that itself results in chronic rejection.⁵

Patient survival differed significantly across our study groups. By five years posttransplant, patients receiving alemtuzumab showed survival rates similar to those receiving Thymoglobulin, and both of these groups showed survival advantages relative to remaining groups. Nevertheless, the Thymoglobulin group had the lowest 5-year *graft* survival rate of all groups, and re-transplantation in the Thymoglobulin patients accounted for the fact that their survival rate was similar to that of alemtuzumab patients. In short, alemtuzumab appears mostly clearly associated with prolonged graft survival (time to loss of initial graft). Consistent with these observations is our finding that only a small number of alemtuzumab patients succumbed to graft failure as a cause of death.

Lastly, the alemtuzumab group had a high freedom from PTLD (96%) comparable to the other three groups, and therefore did not appear to be at increased risk despite its more profound lymphoid depletion. However, in the few instances of EBV mismatch, PTLD developed in all three of the patients who received alemtuzumab whereas it did not develop in all EBV mismatch patients receiving other induction agents or no induction. Although these observations are based on a small number of cases, they suggest caution in alemtuzumab use among such patients. Close monitoring for EBV proliferation via EBV-PCR assays may help identify patients with EBV proliferation at an early stage prior to malignant transformation.

Within our study, it is not possible to determine whether any benefits associated with alemtuzumab induction are attributable to the use of this induction strategy *per se* or to the lower-intensity maintenance immunosuppression regimen that it permitted early posttransplant for our patients (including not only lower dosing by protocol of tacrolimus compared to some of the other study groups, but lower steroid dosing as well). It is noteworthy that all study groups became similar in tacrolimus maintenance dosing levels beyond the first 18 months posttransplant. Despite this convergence, the study groups maintained their differences in patient and graft survival, as well as ACR, LB, OB and BOS well beyond the first 1–2 years posttransplant. Further studies should investigate whether alemtuzumab, combined with an early lower-dose immunosuppression regimen, promotes tolerance or preserves regulatory T cell function and thereby may provide an advantage that persists in the setting of standard long-term maintenance immunosuppression.

Our study has important limitations. Most critically, the immunosuppressive regimens were given sequentially in time, with the alemtuzumab group consisting of the most recent patients. Thus, the improved long-term outcomes for the alemtuzumab group may have been due not to the specific immunosuppression regimen received but to improvements over time in surgical technique, postoperative care, and posttransplant patient management (including, for example, modifications in fungal prophylaxis, CMV prophylaxis and threshold for treatment of ACR). In addition, use of alemtuzumab in conjunction with other bone marrow suppressant medications such as valganciclovir has been associated with increased need for filgrastim.²⁷ Because filgrastim use was not fully documented in all patient groups, we could not evaluate it as an outcome. However, recent analyses of the impact of

valganciclovir prophylaxis (including a subset of the patients from the present alemtuzumab cohort) found that the rate of neutropenia (17%) was within the range of rates previously reported in lung recipients receiving valganciclovir prophylaxis.³⁵ Nevertheless, this issue requires further examination in future studies.

Work is also needed to examine other important outcomes that we did not consider, including infection, which is one of the principal short-term risks with alemtuzumab. We did ascertain that infectious causes of death were not increased in alemtuzumab patients relative to other study groups. Recent analyses of the incidence of blood stream infections and opportunistic infections among organ recipients receiving alemtuzumab (including subsets of patients from the present cohort) found that (a) alemtuzumab did not appear to be associated with increased risk of bloodstream infection with pathogens typically seen in the context of CD4 cell depletion,³⁶ and (b) opportunistic infections were more likely in lung recipients than other transplant recipients but alemtuzumab induction therapy was not an independent risk factor for these infections.³⁷ However, risk of infection associated with alemtuzumab induction in lung transplantation remains a concern clinically^{12,38} and it demands closer scrutiny in future studies.

In the present analyses, we were unable to consider other potentially important outcomes. For example, during the time period of our study, patients were not routinely evaluated for evidence of antibody-mediated rejection and thus it could be not examined using our retrospective methodology. Similarly, during the study time frame, our program did not have protocolized use of azithromycin for the prevention or treatment of BOS, or protocolized treatment of gastroesophageal reflux disease. Treatment for the latter was often dependent on patients' overall clinical status. In general, because our study was a retrospective investigation of medical records, we were unable to test hypotheses for mechanisms explaining differences between groups on study outcomes.

Lastly, we examined patients from a single center, and our individual study groups were relatively small. Furthermore, by relying on data from an existing clinical database, the information available may have been incomplete, despite our attempts to cross-check the information with individual patient records.

In conclusion, attempts to empirically establish the optimal immunosuppression regimen to minimize morbidities and maximize survival in lung transplantation remain limited. Lymphoid-depleting induction therapies with reduced maintenance immunosuppression may provide additional strategies to improve patient care. Our findings suggest that alemtuzumab induction may be associated with long-term benefits both in terms of graft function and survival. Given its increasing use in lung transplantation,¹ randomized controlled trials to rigorously establish the benefits and long-term safety profile of this agent are warranted.

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Appendix

Percentage of patients free of each study endpoint across 5 years posttransplant (rates from Kaplan-Meier analyses).

Outcome by study group	Percentage of patients free of endpoint						
	3 mos.	6 mos.	1 year	2 years	3 years	4 years	5 years
<u>Patient death</u>							
No induction	76	74	71	64	57	52	47
Daclizumab	89	86	80	68	62	51	44
Thymoglobulin	88	88	79	72	67	65	60
Alemtuzumab	95	93	88	76	65	64	59
<u>Graft loss</u>							
No induction	76	74	71	64	57	52	46
Daclizumab	89	86	80	68	62	49	41
Thymoglobulin	86	86	77	67	49	47	44
Alemtuzumab	95	93	88	75	64	63	59
<u>Acute cellular rejection</u>							
No induction	38	32	25	20	20	18	18
Daclizumab	43	30	25	19	19	19	19
Thymoglobulin	39	34	31	20	20	20	20
Alemtuzumab	78	73	63	50	39	35	29
<u>Lymphocytic bronchiolitis</u>							
No induction	91	91	88	80	75	70	70
Daclizumab	91	72	68	62	57	55	55
Thymoglobulin	75	69	67	64	61	58	54
Alemtuzumab	95	93	89	87	85	79	78
<u>Obliterative bronchiolitis</u>							
No induction	97	96	91	84	79	75	69
Daclizumab	99	97	91	82	78	73	70
Thymoglobulin	100	100	94	74	65	65	62
Alemtuzumab	100	100	100	93	90	88	86
<u>Bronchiolitis obliterans syndrome</u>							
No induction	100	100	92	77	70	63	46
Daclizumab	100	98	94	79	62	50	43
Thymoglobulin	97	97	95	62	53	38	27
Alemtuzumab	100	100	97	87	74	67	54
<u>PTLD</u>							
No induction	99	97	97	96	94	94	94
Daclizumab	100	98	97	97	97	97	97
Thymoglobulin	97	97	97	97	97	97	97
Alemtuzumab	99	98	97	97	96	96	96

Figure 1.
Kaplan-Meier 5-year patient survival and graft survival across four study groups.

Figure 2.
Kaplan-Meier 5-year freedom from acute cellular rejection and lymphocytic bronchiolitis across four study groups.

Figure 2. Kaplan-Meier 5-year freedom from obliterative bronchiolitis and bronchiolitis obliterans syndrome across four study groups.

Figure 4.
Kaplan-Meier 5-year freedom from PTLD across four study groups.

Table 1

Maintenance immunosuppression regimens utilized in study groups.

	Study Group			
	No induction (n=93)	Daclizumab (n=73)	Thymoglobulin (n=43)	Alemtuzumab (n=127)
Calcineurin inhibitor	Tacrolimus	Tacrolimus	Tacrolimus	Tacrolimus
Target 12-hour trough level ^a	15–20 ng/mL	15–20 ng/mL	12–15 ng/mL	12–15 ng/mL
Antimetabolite ^b	AZA/MMF/None	AZA/MMF/None	AZA/None	MMF/None
	n = 82/6/5	n = 49/20/4	n = 4/39	n = 60/67
Steroid	20 mg/day ^c	20 mg/day ^c	5 mg/day	5 mg/day

^aTarget trough levels for patients in all groups were gradually reduced over time if patients remained clinically well and free from episodes of acute rejection, with goals of 10–12 ng/mL after 6 months, and 8–12 ng/mL beyond the first year posttransplant.

^bAZA, azathioprine; MMF, mycophenolate mofetil.

^cPatients received a standard steroid taper of methylprednisolone beginning the day of transplantation and extending over 5 days from 240mg/d to 40mg/d, followed by 20mg/d prednisone.

Table 2

Characteristics of lung transplant recipients in the no induction, daclizumab, thymoglobulin, and alemtuzumab groups.

Characteristic	Study Group				Test Statistic ^d
	No induction (n=93)	Daclizumab (n=73)	Thymoglobulin (n=43)	Alemtuzumab (n=127)	
Date of transplant, range ^b	1998 – 2001	2001 – 2002	2002 – 2003	2003 – 2005	
<u>At transplant</u>					
Gender, % male	55.1	52.1	46.5	50.0	1.21
Age, M±SD	51.7 ± 11.0	51.2 ± 12.4	46.4 ± 13.5	52.1 ± 12.7	3.32*
Race, %					
European American	92.5	94.5	95.3	92.1	6.84
African American	5.3	1.4	4.7	7.1	
Other	2.2	4.1	0.0	0.8	
Indication for transplant, %					
COPD/Emphysema	31.6	37.0	30.2	31.4	11.52
Idiopathic Pulmonary Fibrosis	16.3	20.5	11.6	27.3	
Cystic Fibrosis	12.2	15.1	23.3	12.4	
Other	39.8	27.4	34.9	28.9	
Type of transplantation					
Single	67.7	56.2	41.9	38.6	21.84**
Bilateral	28.0	39.7	55.8	55.9	
Heart-lung	4.3	4.1	2.3	5.5	
CMV mismatch (D+/R-), % yes	16.7	31.0	32.6	23.6	6.17
EBV mismatch (D+/R-), % yes	5.7	3.0	7.3	2.6	2.45
Ischemia time, minutes	272.7 ± 86.2	292.8 ± 96.4	347.6 ± 93.5	347.7 ± 88.0	12.52***
Donor age, M±SD	36.9 ± 13.1	36.2 ± 16.5	33.1 ± 14.8	35.4 ± 14.5	0.70
<u>Post-transplant</u>					
Length of stay, transplant admission, days ^c	21 (15–27)	21 (15–27)	32 (26–38)	21 (15–27)	9.44*
Length of ICU stay, transplant admission, days ^c	3 (2–4)	4 (1–7)	7 (4–10)	3 (2–4)	5.76
Number of readmissions per patient/year, first year post-transplant ^d	2.45	1.70	2.46	1.70	12.86**

Characteristic	Study Group				Test Statistic ^d
	No induction (n=93)	Daclizumab (n=73)	Thymoglobulin (n=43)	Alemtuzumab (n=127)	
Measured tacrolimus levels (ng/mL) ^e					
1–6 months	15.1 ± 2.0	13.1 ± 1.8	11.9 ± 1.4	12.7 ± 1.6	35.51***
7–12 months	12.4 ± 2.5	11.0 ± 2.3	9.0 ± 2.0	12.0 ± 2.8	14.35***
13–18 months	11.8 ± 2.2	10.6 ± 2.6	9.6 ± 2.4	11.6 ± 2.9	5.26**
19–24 months	11.6 ± 2.0	10.2 ± 2.6	10.4 ± 2.6	10.7 ± 3.4	1.82
25–30 months	10.9 ± 2.1	10.2 ± 3.2	9.6 ± 2.4	10.5 ± 3.3	1.14
31–36 months	10.4 ± 2.6	10.1 ± 2.2	10.2 ± 2.4	10.3 ± 3.3	0.06
37–42 months	9.9 ± 2.4	9.5 ± 2.9	10.5 ± 2.5	10.0 ± 3.4	0.47
43–48 months	9.6 ± 2.6	8.9 ± 2.1	9.9 ± 3.1	9.2 ± 2.8	0.65
49–54 months	9.1 ± 2.2	9.0 ± 2.6	10.1 ± 2.9	8.4 ± 2.3	2.36
55–60 months	9.2 ± 1.9	9.7 ± 2.7	10.0 ± 4.7	8.5 ± 2.7	1.35
Number of clinically-indicated biopsies per patient-year after conclusion of surveillance period ^{d,f}	1.38	1.19	1.59	1.37	10.22*

* p < .05
 ** p < .01
 *** p < .001

^a χ^2 for categorical variables. For continuous variables, F test for tacrolimus levels, Breslow χ^2 test for length of stay variables; likelihood ratio χ^2 test from poisson regression for readmissions per person year of observation.

^b The date range encompasses the majority of patients in each group. In the daclizumab group, 5 patients were transplanted in 2000, 1 patient in 2003 and 1 patient in 2005 (the last patient received daclizumab instead of alemtuzumab due to concern about possible donor transmission of histoplasmosis).

^c Estimated from Kaplan-Meier analysis in order to adjust for censoring due to patient death; each value is the median number of days and 95% confidence interval around the median estimate.

^d Computed as events per patient-year of observation since patients survived for varying time periods post-transplant.

^e Based on all levels available for all patients during each time period.

^f The biopsy surveillance protocol covered the first two years posttransplant; see text for more description.

Table 3

Causes of lung transplant recipient deaths, n (%).

Causes of death	Total deceased sample (n=159)	Study groups				Fisher's Exact p ^a
		No induction (n=49)	Daclizumab (n=41)	Thymoglobulin (n=17)	Alemtuzumab (n=52)	
Infection	56 (35.2)	18 (36.7)	12 (29.3)	8 (47.1)	18 (34.6)	.620
Graft failure	42 (26.4)	17 (34.7)	14 (34.1)	4 (23.5)	7 (13.5)	.045
Pulmonary^b	15 (9.4)	3 (6.1)	2 (4.9)	2 (11.8)	8 (15.4)	.279
Malignancy^c	15 (9.4)	3 (6.1)	6 (14.6)	1 (5.9)	5 (9.6)	.577
Cardiovascular	10 (6.3)	5 (10.2)	1 (2.4)	0 (0.0)	4 (7.7)	
Other	10 (6.3)	2 (4.1)	3 (7.3)	0 (0.0)	5 (9.6)	
Cerebrovascular	6 (3.8)	1 (2.0)	1 (2.4)	2 (11.8)	2 (3.8)	
Unknown	5 (3.1)	0 (0.0)	2 (4.9)	0 (0.0)	3 (5.8)	

^aTested only for the four most common causes of death occurring in > 10% of the sample due to sparse cells within multiple groups for remaining causes. Each test compares whether the distribution of deaths due to a given cause (vs. all other causes) differs across the four study groups.

^bPulmonary includes bronchiolitis, pulmonary embolism, respiratory failure, acute respiratory distress syndrome, and primary pulmonary hypertension.

^cIncludes 4 cases of PTLID, one in each study group.