Delayed Development of Obliterative Bronchiolitis Syndrome With OKT3 After Unilateral Lung Transplantation* 

A Plea for Multicenter Immunosuppressive Trials

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There is no consensus regarding the optimal induction immunosuppression regimen after lung transplantation (LT). In addition to the potential benefit of a reduced incidence of early acute allograft rejection, cytolytic induction immunosuppression may impact on long-term allograft function. We retrospectively assessed our incidence of obligatorive bronchiolitis syndrome (OBS) stages Ia and IIa in LT survivors given two different cytolytic induction immunosuppression regimens: (between March 1989 and October 1990) OKT3 (5 mg/d)x10 to 14 days (n=11) vs (between November 1990 and April 1993) Minnesota antilymphocyte globulin (MALG) (10 to 15 mg/kg/dx5 to 7 days. Cyclosporine (CSA) (whole blood polyclonal assay=600 to 800 ng/mL), azathioprine (1 to 2 mg/kg/d), and maintenance prednisone (0.2 mg/kg/d) were similar. Surveillance spirometry was performed monthly, in accordance with accepted American Thoracic Society criteria. Fiberoptic bronchoscopy with transbronchial biopsies (TBBs) were performed for clinical indications. Surveillance TBBs were not performed during the era of this study. As defined by the ISHLT “Working Formulation for the Standardization of Nomenclature and for Clinical Staging of Chronic Dysfunction in Lung Allografts,” latencies to development of OBS stages Ia and IIa were determined by Kaplan-Meier analysis. Stepwise regression (Cox proportional hazards model) was performed for the variables: cytolytic induction regimen, episodes cytomegalovirus (CMV) pneumonitis, episodes CMV infection, serologic CMV donor (+): recipient (-) mismatch, prior pregnancy, HLA (A,B,DR±DQ) mismatches, episodes greater than grade A1 acute cellular rejection (ACR). We found that the OKT3 cohort experienced longer latencies for OBS stages Ia and IIa. Latencies to OBS stage Ia for OKT3 vs MALG were 962±65 vs 354±85 days (X±SEM) respectively. Brookmeyer-Crowley 95% confidence intervals for median latencies were 744 to 1,180 vs 266 to 510 days for OKT3 vs MALG, respectively. The Cox model was significant only for the variable of the induction cytolytic immunosuppression regimen (p=0.0015). By physiologic criteria, a longer course of OKT3 appeared superior to the short-course MALG protocol in delaying chronic lung allograft dysfunction. These effects may be related either to inherent differences in the antilymphocyte preparations or, alternatively, the difference in duration of treatment between groups. Surveillance TBB and treatment of detected occult ACR may serve to negate the observed differences in latencies for OBS.

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Lung transplantation (LT) is now routinely performed for a spectrum of end-stage cardiopulmonary maladies, while obliterative bronchiolitis (OB)

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has emerged as the primary cause of late morbidity and mortality.1-4 OB is characterized clinically by a progressive decline in spirometric indexes of expiratory airflow. The concept that OB represents a manifestation of chronic lung allograft rejection is supported by the presence of donor-specific alloreactive T-lympho-
cytolytic induction is necessary after lung transplantation. A potential advantage of induction cytolytic immunosuppression is that it allows for a “window” of time to optimize cyclosporine (CSA) levels, and, thereby, possibly reduce the incidence and/or severity of early allograft rejection. The frequency and severity of acute rejection episodes have been associated with the propensity for OB. Therefore, cytolytic induction therapy may serve to delay or prevent this prevalent long-term complication after LT. Therefore, we have retrospectively determined our incidence of OBS (stages I and II) in unilateral LT survivors who received two different induction immunosuppression regimens.

**MATERIALS AND METHODS**

Between March 1989 and October 1990 (n=11), OKT3, 5 mg/d (Ortho Biotech, Inc; Raritan, NJ) was given for 10 to 14 days as part of a quadruple immunosuppression protocol that included azathoprine, prednisone (PRED), and CSA. Our subsequent quadruple immunosuppressive protocol between November 1990 and April 1993 (n=13) used Minnesota antilymphocyte globulin (MALG), 10 to 15 mg/kg/d for 5 to 7 days, instead of OKT3.

T-cell crossmatches were negative in all cases. CSA was administered in both regimens to achieve a polyclonal whole blood level of 600 to 800 ng/mL (Abbott TDX; Abbott Park, III), and azathoprine was administered at 2 mg/kg/d and subsequently adjusted to maintain a WBC count of 4,000/mm³ or more. Daily oral PRED therapy (1.0 mg/kg/d) was commenced upon completing cytolytic therapy in both groups. PRED dosage was decreased 0.1 mg/kg/wk to a maintenance dosage of 0.2 mg/kg/d. Surveillance spirometry was performed with both patient-performed microspirometry (Micro Medical Ltd; Kent, England) as well as during each transplant clinic visit (using a Cardiopulmonary Instruments model 22) and using accepted American Thoracic Society criteria. Fiberoptic bronchoscopy with BAL and TBB specimens were obtained for clinical indications or a decrement of 10% in FVC and/or FEV₁. During the era of this study, surveillance TBBs were not performed in asymptomatic recipients. The TBB specimens were categorized in accord with definitions established by the Lung Rejection Study Group. Episodes of acute rejection (≥grade A₁) were treated with three consecutive days of IV methylprednisolone (1 g). Histologic evidence of OB (grade C) or episodes of spirometric decrement when associated with “nonspecific” histologic type, in the absence of cytomegalovirus (CMV), were also treated with methylprednisolone. CMV prophylaxis was administered to all recipients except for serologic donor-negative and recipient-negative cases. Prophylaxis included ganciclovir, 5 mg/kg every 12 h for 3 weeks, and daily for 1 week of maintenance therapy (adjusted for renal function).

**Table 1—Variables Examined by Cox Proportional Hazards Model for MALG vs OKT3 Groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>MALG (n=13)</th>
<th>OKT3 (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV pneumonitis episodes (12 mo)</td>
<td>0.62±1.19</td>
<td>1.27±1.35</td>
</tr>
<tr>
<td>CMV infection episodes (12 mo)</td>
<td>0.08±0.28</td>
<td>0.27±0.65</td>
</tr>
<tr>
<td>Donor CMV+ serologic status</td>
<td>0.69</td>
<td>0.73</td>
</tr>
<tr>
<td>Recipient CMV+ serologic status</td>
<td>0.69</td>
<td>0.64</td>
</tr>
<tr>
<td>CMV Donor/recipient mismatch (D+/R−)</td>
<td>0.08</td>
<td>0.18</td>
</tr>
<tr>
<td>Previous pregnancy</td>
<td>0.38</td>
<td>0.45</td>
</tr>
<tr>
<td>No. of HLA (A,B,DR) matches</td>
<td>1.46±1.07</td>
<td>1.14±0.69</td>
</tr>
<tr>
<td>No. of HLA (A,B,DR,DQ) matches</td>
<td>2.08±1.32</td>
<td>2.14±0.94</td>
</tr>
<tr>
<td>Episodes AR &gt;grade A₁ (12 mo)</td>
<td>2.23±1.79</td>
<td>1.64±1.12</td>
</tr>
</tbody>
</table>

*All p values are not significant.

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21730/ on 03/31/2017)
followed by high-dosage acyclovir, 800 mg three to five times per day po for 3 to 6 months posttransplantation. Although “first-dose” reactions were frequently observed with OKT3 (hypoxemia, hypoperfusion, and hemodynamic alterations), there was no significant morbidity or associated mortality.

**RESULTS**

Native lung diseases for the MALG group included emphysema (46.2%), interstitial pulmonary fibrosis (38.5%), and primary pulmonary hypertension (15.4%), while they were not statistically different for the OKT3 group, specifically, 27.3%, 36.4%, and 18.2%, respectively. Proportions of patients with histologically confirmed OB (grade C) were 77% (10 of 13 patients) for MALG and 65% (7 of 11 patients) for OKT3 (p=NS). Table 1 demonstrates the variables that were examined by stepwise regression (Cox proportional hazards model). There were no significant differences between MALG and OKT3 groups for any of these variables by Mann-Whitney rank sums (p=NS).

Figure 1 demonstrates, by Kaplan-Meier analysis, the proportion of patients who have demonstrated OBS stage I. Although no statistical difference was discerned in regard to the ultimate incidence, the OKT3 group experienced a longer latency until development of OBS stage I (Mantel-Cox; p<0.001). The median (50th) quartiles for MALG vs OKT3 groups for development of OBS stage I were 354±85 (estimate±SE) and 962±65 days, respectively. Brookmeyer-Crowley 95% confidence interval for the median time to OBS stage I was 266 to 510 days for MALG and 744 to 1,180 days for the OKT3 group.

In Figure 2, a similar analysis is illustrated for the proportion of patients with OBS stage II, or death. Four deaths occurred in each treatment group, and postmortem examination demonstrated OB in all patients. Death occurred 369±56 days (X±SEM) (range, 298 to 532 days) for the MALG group, as compared with 826±243 days (range, 217 to 1,349 days) for the OKT3 group. One episode of cutaneous and visceral Epstein-Barr virus-associated post-transplant lymphoproliferative disease occurred in an OKT3 recipient. As demonstrated in Figure 2, the time latency until development of OBS stage II was significantly longer for the OKT3 group (Mantel-Cox; p<0.05). Stepwise regression demonstrated that only the immunosuppression variable was statistically significant (p=0.0015) for OBS stage I and II, while the variables outlined in Table 1 were not significant.

**DISCUSSION**

The primary finding of our retrospective analysis was longer latencies in development of OBS stages I and II in the cohort who received 10 to 14 days of induction with OKT3, compared with 5 to 7 days of MALG.

Previous studies performed in cadaveric renal transplantation have demonstrated no significant differences in graft survival or function when comparing induction immunosuppression using OKT3 vs either MALG or rabbit antithymocyte globulin (RATG). However, clinical follow-up has been generally limited to only 1 year posttransplantation. For thoracic organ transplantation, there has been no consensus regarding the role of induction cytolytic immunosuppression. Numerous transplant centers have opted to avoid cytolytic immunosuppression due to concerns of promoting either CMV or fungal infections, as well as the significant costs associated with these therapies. To our knowledge, however, there has been no study that has addressed the impact of either the type or duration of induction immunosuppression on long-term lung allograft function. In one preliminary report by Demirtzis et al., although survival was not different, the actuarial freedom of OB 2 years posttransplantation was 28±4% in an LT cohort who received prophylactic T-cell antibodies, as compared with 7±5% in a group with standard triple-drug immunosuppression. A recent report by Reinsmoen et al. has demonstrated differences in BAL fluid-primed lymphocyte testing (PLT) for donor HLA class I and II in recipients with OB. Whereupon progressive disease was associated with a donor class I antigen-specific primed lymphocyte testing, class II specificity was indicative of more indolent disease. However, of interest also was that the course of induction immunosuppression varied considerably in their study. MALG was used in approximately two thirds of their patients, with a duration of 2 to 7 days.

In our analysis, the 10 to 14-day course of treatment
(OKT3 group) was superior to 5 to 7 days (MALG group) in preserving long-term allograft function. Differences in latencies for OBS may be related either to the specific antilymphocyte preparations that were used or, alternatively, to the duration of treatment. In view of data obtained in renal transplantation that had compared OKT3 with polyclonal preparations, the latter mechanism would appear more probable.\textsuperscript{19,20} Furthermore, our group has recently reported different patterns of spirometric deterioration with OBS, which may in fact be related to the specific induction immunosuppression regimen.\textsuperscript{23}

Our study certainly suffers from the retrospective nature of our analysis and the relatively small numbers of patients that were available for study. Therefore, small differences between the treatment groups may have contributed to a type II error in assessing differences in possible risk factors for OBS (eg, number of episodes of CMV).

Furthermore, since we did not perform surveillance TBIs during the era of this study, we could not determine whether OKT3 decreased the incidence of asymptomatic episodes of acute rejection and, hence, delayed development of OBS. Detection and treatment of occult episodes of acute rejection may serve to negate the observed differences between OKT3 and MALG. We believe that our data are compelling and warrant further investigation, vis-à-vis the specific type and duration of induction cytolytic immunosuppression. These data emphasize the need in LT for well-designed, controlled, multicenter clinical trials.

REFERENCES