Long-Term Outcomes following Alemtuzumab Induction in Lung Transplantation

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ABSTRACT

Objectives: Alemtuzumab is a commonly used induction agent for solid-organ transplantation. Its use in lung transplantation with reduced immunosuppressive regimens, however, has yet to be well characterized.

Methods: From November 2006 to March 2008, 20 consecutive lung transplantation patients received alemtuzumab induction with a reduced maintenance immunosuppression regimen. Twenty consecutive case-controls who underwent transplantation between 2005 and 2006 were treated with a standard immunosuppression regimen without induction. Outcome variables were patient survival, acute rejection, infection, and bronchiolitis obliterans syndrome.

Results: Mean follow-up time was 1400 days in the alemtuzumab group and 1210 days in the control group. Double lung transplantation was performed in 21 patients (12 in the alemtuzumab group and 9 in the control group). There was no difference in survival between the alemtuzumab (n = 10) and control (n = 10) groups. There was also not a significant difference in time-adjusted death based on Kaplan-Meier analysis. The mean number of any grade of rejection event per patient was not significantly different (alemtuzumab 2.3 ± 2.7 vs. control 3.2 ± 2.35; P = .22). There was a trend toward the reduced incidence of infection requiring intravenous antibiotics per patient (alemtuzumab 2.4 vs. control 3.8; P = .08). The incidence of bronchiolitis obliterans syndrome was similar in both groups (alemtuzumab 55% vs. control 70%; P = .25).

Conclusions: Alemtuzumab induction with reduced immunosuppression offers a comparable 5-year survival and rejection rate compared to standard-dose immunosuppression regimen.

INTRODUCTION

Optimal immunosuppressive therapy for lung transplant recipients has been a topic of much debate and research over the past 2 decades since lung transplantation has become a recognized modality for management of end-stage lung disease. Increased availability and diversity of immunosuppressive agents has led to an increase in lung transplantation survival, but declining pulmonary function, recurrent infections, and bronchiolitis obliterans syndrome (BOS) remain major limiting factors [Christie 2011]. The use of induction therapy with alemtuzumab (Campath-1H; Genzyme, Cambridge, MA, USA) has demonstrated reduced rates of infection and rejection as well as improved survival in solid organ transplantation [McCary 2005; Zeevi 2007; Hanaway 2011; Shyu 2011]. Investigators at the University of Pittsburgh have found that acute and chronic rejection rates were reduced following alemtuzumab induction using similar maintenance immunosuppressive drug regimens as our own [Christie 2011]. Furthermore, in our previous study, we compared the early outcome of lung transplant recipients receiving induction therapy with alemtuzumab and a reduced immunosuppression regimen to those receiving standard immunosuppression and found that early rejection and infection rates as well as early survival were equivalent [B.W., unpublished data, 2010]. However, follow-up from that study was only 1 year, and the long-term impact of alemtuzumab induction on lung transplantation outcomes is not well known. In this study, we sought to determine the effects of alemtuzumab induction with reduced immunosuppression by comparing the rates of rejection, infection, pulmonary function, and survival after a follow-up period of approximately 5 years.

MATERIALS AND METHODS

Study Participants

This case-control study was performed at the University of Maryland Medical Center. Patients provided informed consent for alemtuzumab induction therapy. Institutional review board approval was obtained. Between November 2006 and March 2008, 20 consecutive lung transplantation patients received alemtuzumab induction with reduced maintenance immunosuppression. Twenty consecutive patients who received transplantations immediately prior to the study period were chosen to as controls and received standard immunosuppression.
Immunosuppressive Protocol and Infection Prophylaxis

Patients in both groups received 125 mg of methylprednisolone before allograft reperfusion then every 8 hours for 3 total doses. Alemtuzumab (30 mg) was infused over 2 hours within 12 hours after transplantation. Acetaminophen 650 mg, diphenhydramine 50 mg, and methylprednisolone 500 mg intravenously were administered as premedications in both groups. In the alemtuzumab group, maintenance immunosuppression included tacrolimus (target level 10-15 ng/mL), mycophenolate mofetil (MMF) 250 mg twice daily and prednisone 7.5 mg daily on postoperative day 1. Control patients were treated with standard dose immunosuppression comprising tacrolimus (target level 10-15 ng/mL), MMF 1 gram twice daily, and prednisone 20 mg daily.

Patients who were mismatches for cytomegalovirus (CMV) received valganciclovir 900 mg daily for 6 months. All other CMV combinations received valganciclovir 450 mg daily for 6 months. Fungal prophylaxis consisted of voriconazole 200 mg twice daily for 6 months.

Table 1. Characteristics of Lung Transplant Recipients in the Alemtuzumab and Control Groups*

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n = 20)</th>
<th>Alemtuzumab Group (n = 20)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (55%)</td>
<td>11 (55%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Female</td>
<td>9 (45%)</td>
<td>9 (45%)</td>
<td></td>
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<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>African-American</td>
<td>7 (35%)</td>
<td>9 (45%)</td>
<td>0.519</td>
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<tr>
<td>Caucasian</td>
<td>13 (65%)</td>
<td>11 (55%)</td>
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<tr>
<td>Age, y (mean ± standard deviation)</td>
<td>56.1 ± 11.7</td>
<td>57.9 ± 11.9</td>
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<tr>
<td>Transplant type, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Single</td>
<td>11 (55%)</td>
<td>8 (40%)</td>
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</tr>
<tr>
<td>Double</td>
<td>9 (45%)</td>
<td>12 (60%)</td>
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<td>Underlying disease, n (%)</td>
<td></td>
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</tr>
<tr>
<td>ILD</td>
<td>14 (70%)</td>
<td>11 (55%)</td>
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<tr>
<td>COPD</td>
<td>5 (25%)</td>
<td>6 (30%)</td>
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<tr>
<td>A1A deficiency</td>
<td>5 (1%)</td>
<td>0 (0%)</td>
<td></td>
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<tr>
<td>PAH</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td></td>
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<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>CMV D+/R–, n (%)</td>
<td>6 (30%)</td>
<td>5 (25%)</td>
<td>0.723</td>
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<tr>
<td>EBV D+/R–, n (%)</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>0.487</td>
</tr>
<tr>
<td>PRA &gt; 10%, n (%)</td>
<td>4 (20%)</td>
<td>7 (35%)</td>
<td>0.288</td>
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<td>HLA mismatch number (mean ± standard deviation)</td>
<td>5.0 ± 1.2</td>
<td>5.1 ± 0.8</td>
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<td>Donor age, y (mean ± standard deviation)</td>
<td>28.1 ± 12.2</td>
<td>29.5 ± 12.8</td>
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<tr>
<td>Follow-up period, d</td>
<td>1504</td>
<td>1111</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*ILD indicates interstitial lung disease; COPD, chronic obstructive lung disease; A1A, alpha 1 antitrypsin; PAH, pulmonary arterial hypertension; CMV, cytomegalovirus; D+, donor positive; R–, recipient negative; EVB, Epstein-Barr virus; PRA, panel reactive antibody; HLA, human leukocyte antigen.

Posttransplantation Monitoring

Bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy was performed every 3 months posttransplantation for 1 year and when clinically indicated after the first posttransplantation year. Pulmonary function testing was performed at discharge and at 3-month intervals for the first postoperative year in accordance with American Thoracic Society standards. BOS was defined as a sustained decrease in forced expiratory volume in 1 second (FEV1) of at least 20% from the individual patient’s maximum values [Estenne 2002].

Data Collection

Data analysis for defined parameters was performed for each patient at approximately 5 years posttransplantation by collection of biopsy results and pulmonary function tests (PFT) along with antibiotic cycles. Both paper and electronic medical records were reviewed and entered into a database for analysis. Infections and cycles of intravenous antibiotics were recorded for all patients. Infection was considered significant if it required antibiotic therapy.
Statistical Methods

Survival rate, incidence of infection, and chronic rejection were analyzed by the method of Kaplan and Meier and assessed by log-rank test. Either death or re-transplantation was considered a study event. Continuous variables were compared using Mann-Whitney U-test for non-parametric data. P values were reported as 2-tailed and considered significant if less than .05. Values were reported as means and standard deviations (SD). Data analyses were conducted with the use of SPSS 20.0 (IBM Corporation; Armonk, NY, USA) and Microsoft Excel software (Redmond, WA, USA).

RESULTS

Demographics

Baseline demographics are shown in Table 1. Double lung transplantation was performed in 21 patients (12 in the alemtuzumab group and 9 in the control group); all other patients underwent single lung transplantation. One patient in each group underwent re-transplantation.

Follow-up

All patients were followed until reaching a primary endpoint, which was defined as either death or re-transplantation. No patient was lost to follow-up. Mean duration of follow-up from induction to endpoint was 1111 days in the alemtuzumab group and 1504 days in the control group (P = .5).

Patient and Graft Survival

There was no significant difference in patient or graft survival between the groups at 5 years. Both groups had a survival of 50% at 5 years (Figure 1). Graft survival was 50% in both groups at 5 years (P = .74).

Pulmonary Function

The average number of PFTs analyzed per patient was 16.7 (18.8 in the alemtuzumab group and 14.61 in the control group). One patient in each group was excluded from analysis of pulmonary function due to lack of pulmonary function data as a result of early posttransplantation mortality. The alemtuzumab group showed a significantly slower decline in FEV1 (128 mL/y in the alemtuzumab group vs. 263 mL/y in the control group, P = .04). After adjustment for type of transplantation, the alemtuzumab group continued to show slower decline in single (89 mL/y in the alemtuzumab vs. 270 mL/y in the control group) as well as double lung transplant recipients (169 mL/y in the alemtuzumab group vs. 251 mL/y in the control group). Although not statistically significant, an earlier peak FEV1 was also observed in the alemtuzumab group (239 days in the alemtuzumab group vs. 322 days in the control group, P = .3).

Bronchiolitis Obliterans Syndrome

Incidence of BOS was similar in the alemtuzumab and control groups who received standard immunosuppression (57.9% in the alemtuzumab group vs. 73.7% in the control group; P = .56; Figure 2). Double lung transplant recipients showed much lower incidence of BOS (36.4%) in the alemtuzumab group when compared to control group (88.9%, P = .7; Figure 3), and an almost opposite trend was seen in single lung transplant recipients (Figure 4).

Infection

The alemtuzumab group demonstrated a trend toward fewer infections per patient (2.40 in the alemtuzumab group and 3.85 in the control group; P = .08). A subgroup analysis revealed that patients in the control group suffered from an
average of 3.1 episodes of pneumonia requiring intravenous antibiotics compared to 1.9 episodes per patient in the alemtuzumab group (P = .16).

Histological Rejection

All transbronchial biopsy results were reviewed. Patients in the alemtuzumab group underwent a total of 46 biopsies in the study period compared to 72 biopsies in the control group. Fewer rejection episodes per patient as well as an increased freedom from rejection were observed in the alemtuzumab group, but these differences did not reach statistical significance (Table 2). The alemtuzumab group was less frequently diagnosed with any grade of rejection on surveillance biopsies, but this result did not reach statistical significance (mean 2.3 ± 2.7 in the alemtuzumab group vs. mean 3.2 ± 2.3 in the control group; P = .22).

DISCUSSION

This study represents the long-term follow-up of patients from our initial study comparing alemtuzumab induction therapy combined with low-dose maintenance immunosuppression to standard immunosuppression without induction in lung transplantation. Our early results from that study demonstrated comparable 6- and 12-month survival to the control group and results from the International Society for Heart & Lung Transplantation (ISHLT) registry. At approximately 5 years of follow-up, this study demonstrates that alemtuzumab...
induction and reduced immunosuppression have comparable outcomes to standard high-dose immunosuppressive therapy. We have shown equivalent survival, incidence of BOS, incidence of rejection, and incidence of infection between those receiving alemtuzumab and low-dose immunosuppression with no induction. We also demonstrate a significantly slower decline in FEV1 in the alemtuzumab group. The cause of this may be multifactorial and related to the lower incidence of infection and fewer episodes of rejection observed in this study. Five-year survival in the alemtuzumab group was 50%, which is comparable to the 5-year survival reported by the 2011 ISHLT registry of 53% [Christie 2011]. We believe these are important findings because higher immunosuppressive doses and levels have been shown to correlate with increasing morbidity and mortality [Allan 2004].

Since our initial study began enrollment in 2008, the benefits of induction therapy in solid organ transplantation have been clearly demonstrated [Ailawadi 2008; Hachem 2008; Cai 2010]. Specifically, alemtuzumab, the humanized form of a potent rat immunoglobulin (Ig) M antibody, has been shown to offer equivalent organ and patient survival with a reduced immunosuppressive regimen in both kidney and lung transplantation [McCurry 2005; Zeevi 2007; Hanaway 2011; Shyu 2011]. McCurry et al initially compared the use of induction therapy using thymoglobulin, daclizumab, and alemtuzumab to standard immunosuppressive regimen without induction and found that alemtuzumab was superior to other agents in terms of increased survival and freedom from rejection at 1 year [McCurry 2005]. A 5-year follow-up from the same center showed that patients treated with alemtuzumab induction had better long-term results when compared to other induction agents or no induction therapy with respect to incidence of acute cellular rejection, lymphocytic bronchiolitis, and obliterative bronchiolitis [Shyu 2011].

These findings provide further evidence that induction with alemtuzumab using a reduced immunosuppressive regimen is equivalent or superior to standard immunosuppression without induction in lung transplantation. Additionally, the trend for pulmonary functions was noted to be different among the alemtuzumab group with respect to single and double lung transplantsations. Limitations to this study included the small sample size and use of a case-control experimental design rather than a prospective randomized trial. A large randomized trial comparing alemtuzumab or other induction therapy with standard immunosuppressive therapy has yet to be performed in lung transplantation, but these results contribute to the growing body of evidence in support for such a trial.

ACKNOWLEDGMENTS

The authors would like to thank the patients involved in this study and their families.

REFERENCES