Total Lymphoid Irradiation for Refractory Acute Rejection in Heart-Lung and Lung Allografts*

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Persistent or recurrent acute allograft rejection (AR) refractory to high-dose steroid therapy can adversely affect long-term outcomes of heart-lung (HLT), bilateral-lung (BLT), and single-lung (SLT) transplantations. The use of total lymphoid irradiation (TLI) for the management of refractory acute AR in six transplant recipients (two men, four women; mean age, 29.8 ± 3.8 years) is detailed. There are two HLT (primary pulmonary hypertension [PPH], cystic fibrosis [CF]), 1 BLT (pulmonary hypertension postventricular septal defect repair), and 3 SLT (sarcoid, PPH, congenital heart disease with atrial septal defect) recipients. Refractory AR is defined as persistent rejection unresponsive to high-dose steroid therapy in all cases. The BLT and SLT recipients had at least two moderate and one mild AR events per patient. The HLT recipients had at least two moderate acute heart and one severe and one mild asynchronous acute lung rejection events per patient. A total of 800 cGy of total lymphoid irradiation (TLI) was administered over a 5-week period. Mild and transient leukopenia was the only observed side effect. The patient with PPH received TLI 313 days after HLT for recurrent AR at another institution and died of ARDS 4 weeks after completing TLI. The patient with CF received TLI 707 days after HLT and died 457 days after TLI of severe obliterative bronchiolitis (OB) with multiorgan failure. The patient with BLT received TLI 176 days after transplant and died 372 days after TLI of respiratory failure related to severe rejection. One patient with SLT received TLI 78 days after transplant and died 679 days after TLI of severe acute AR. The two remaining patients with SLTs have been free from acute AR for more than 4 years. The patient with sarcoidosis received TLI 37 days after SLT following a clinical rejection event and two severe acute AR events. He is alive with normal lung function 5 years later. The patient with PPH received TLI 108 days after SLT following three moderate acute AR events and is alive with stable OB 4 years later. These limited preliminary results suggest that TLI has merit for the treatment of intractable acute AR following HLT and lung transplantation. (CHEST 1996; 109:1184-89)

Key words: acute lung rejection; immunosuppression; lung transplantation; radiotherapy; total lymphoid irradiation

Abbreviations: AR = acute allograft rejection; ASD = atrial septal defect; BLT = bilateral-lung transplantation; CF = cystic fibrosis; CMV = cytomegalovirus; HLT = heart-lung transplantation; IR = ionizing radiation; LT = lung transplantation; MP = methylprednisolone; OB = obliterative bronchiolitis; POD = postoperative day; PPH = primary pulmonary hypertension; SLT = single-lung transplantation; TLI = total lymphoid irradiation; VSD = ventricular septal defect

Acceptable long-term results have been achieved with heart-lung transplantation (HLT) and lung transplantation (LT) using conventional immunosuppression (cyclosporine, azathioprine, and prednisone). More than 4,000 such procedures1 have been performed worldwide since 1981. Although death from acute allograft rejection (AR) is rare, it is a significant management issue in this group of patients.2 Obliterative bronchiolitis (OB) or the bronchiolitis obliterans syndrome has emerged as the leading cause of morbidity and mortality in long-term survivors.3 Some reports have shown that the development of OB is directly related to the frequency and intensity of AR events.4,5 AR is generally managed effectively with IV methylprednisolone (MP) in combination with augmentation of oral prednisone dosage and optimization of cyclosporine and azathioprine dosing. Patients occasionally develop recurrent or persistent high-grade AR events refractory to augmented conventional immunosuppression. These patients receive repeated

For editorial comment see page 1136

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administrations of high-dose IV corticosteroids, polyclonal or monoclonal anti-T-cell antibodies, or other immunosuppressive agents (including methotrexate and cyclophosphamide) in an attempt to arrest these repetitive or unremitting AR episodes. This intense immunosuppressive therapy leads to a greater risk of developing serious infections primarily related to cytomegalovirus (CMV), Gram-negative bacteria, and opportunistic fungi. The adverse effects of steroids may further contribute to morbidity complications. Low-dose total lymphoid irradiation (TLI) has been used as a potent immunosuppressive modality with minimal toxicity for recalcitrant AR in heart transplantation.6–10

Ionizing radiation (IR) delivered in the form of high-dose TLI induces a sustained impairment of cellular immunity in patients with Hodgkin's disease. TLI has been successfully employed as an immunosuppressant in small and large animal transplantation studies. It has been effectively used in human bone marrow and kidney allograft transplantation. Also, it has been shown to promptly resolve intractable cardiac allograft rejection in a small number of heart recipients and to provide favorable sustained immunomodulation in this population. To our knowledge, this report details the first case series of TLI in LT for the treatment of refractory acute cellular rejection in six HLT and LT recipients.

**Materials and Methods**

*Patients*

Twenty-seven HLTs, 11 single-lung transplants (SLTs), and 6 bilateral-lung transplants (BLTs) in adults (age >18 years) were performed between August 1989 and January 1992. Six of these patients (TLI group) received TLI after repeated IV boluses of MP and optimization of cyclosporine and azathioprine therapy failed to reverse repetitive or intractable acute cellular rejection. Twenty-three of the 38 patients (rej ector group) had at least one AR that required MP bolus therapy. The remaining 15 patients (nonrejector group) never received pulsed MP and were essentially free from acute cellular rejection. All groups initially received induction immunosuppression with either polyclonal or monoclonal anti-T-cell antibody therapy and conventional immunosuppression. All groups were followed up and events were recorded until February 1995.

Routine surveillance and clinically indicated transbronchial lung biopsies, right ventricular endomyocardial biopsies (HLT recipients), and pulmonary function studies were performed on all recipients as previously described.11 AR was classified according to the histologic standards established by the Lung Rejection Study Group.12 All grade 2 or higher ARs were treated with MP (15 mg/kg daily for 3 consecutive days). Clinical ARs were defined by fever, respiratory symptoms, radiographic infiltrates, and prompt resolution with IV MP without morphologic confirmation.

Patients were treated with TLI for unremitting AR (defined as unresolved persistent perivascular lymphocytic infiltration following three courses of MP) or three recurrent AR episodes (defined as episodes of AR, each separated by a rejection-free biopsy).

**Irradiation Procedure**

The TLI regimen was modeled according to the description by Levin et al.9 It consisted of a midplane dose of 50 cGy administered on a 6-MeV linear accelerator by an anterior-posterior opposed technique per treatment, with two treatments per week for a total of 500 cGy. The radiation was directed at the upper (mantle) and lower (‘‘inverted-Y’’) fields as previously described.9 The mantle field included the submental, submandibular, cervical, supraclavicular, infracavicular, and axillary nodes bilaterally, as well as the mediastinal and hilar nodes, and the thymus. The inverted-Y field included the para-aortic, iliac, and inguinal-femoral lymph nodes, and the entire spleen.

Azathioprine dosage was temporarily reduced or discontinued during the course of TLI. TLI was interrupted or discontinued if intercurrent infection or severe leukopenia (defined as a total WBC count <3,000/mm³) developed. Five of the six patients tolerated the treatment well, with no splits or interruptions. One patient had a brief late interruption because of severe leukopenia and *Pneumocystis carinii* pneumonia but still completed the TLI. One patient received an additional course of TLI that was discontinued because of CMV viremia. All patients gave informed consent for TLI, as approved by the Stanford University Medical Center Committee for the Protection of Human Subjects.

**Statistical Analysis**

Differences in the WBC and azathioprine dose before, immediately following completion of TLI, and 3 months after TLI were analyzed by the Friedman test. Differences in the number of rejection events before and after TLI were analyzed by the Mann-Whitney U test. All p values were based on two-sided tests, and p values <0.05 were considered statistically significant.

**Results**

The clinical data of the patients who received TLI for refractory rejection are summarized in Table 1. Briefly, there were four women and two men ranging in age from 26 to 34 years with a mean and SD of 29.8 ± 3.8. Table 2 summarizes the TLI specifications. The median pre-TLI period was 142 days (range, 37 to 707 days). The mean duration and SD of TLI was 34 ± 4 days. The median post-TLI period to February 1, 1995

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**Table 1—Characteristics of Patients Requiring TLI***

<table>
<thead>
<tr>
<th>Patient No./ Sex</th>
<th>Underlying Diagnosis</th>
<th>Transplant Type</th>
<th>CMV-D</th>
<th>CMV-R</th>
<th>Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/33/F</td>
<td>CF</td>
<td>HLT</td>
<td>Neg</td>
<td>Neg</td>
<td>RATG</td>
</tr>
<tr>
<td>2/25/M</td>
<td>PPH</td>
<td>HLT</td>
<td>Neg</td>
<td>Neg</td>
<td>OKT3</td>
</tr>
<tr>
<td>3/32/M</td>
<td>Sarcoïdosis</td>
<td>L-SLT</td>
<td>Neg</td>
<td>Neg</td>
<td>OKT3</td>
</tr>
<tr>
<td>4/34/F</td>
<td>ASD-Eisenmenger’s</td>
<td>R-SLT with ASD repair</td>
<td>Neg</td>
<td>Neg</td>
<td>OKT3</td>
</tr>
<tr>
<td>5/29/F</td>
<td>PPH</td>
<td>L-SLT</td>
<td>Neg</td>
<td>Pos</td>
<td>OKT3</td>
</tr>
<tr>
<td>6/26/F</td>
<td>Eisenmenger’s with VSD repair</td>
<td>BLT</td>
<td>Pos</td>
<td>Pos</td>
<td>OKT3</td>
</tr>
</tbody>
</table>

*ASD=atrial septal defect; VSD=ventricular septal defect; neg=negative; pos=positive.
was 568 days (range, 51 to 1,937 days). The overall median survival time in this period was 998 days (range, 390 to 2,008 days). Patient 3 developed mild P. carinii pneumonia and responded to full-dose trimethoprim-sulfamethoxazole therapy. This briefly interrupted his TLI therapy, which he subsequently completed. Patient 2 died of ARDS of unknown etiology within weeks of completing TLI. There was no evidence of rejection at autopsy.

Table 3 demonstrates the effect of TLI and azathioprine on peripheral WBC parameters. The mean pre-TLI, immediate post-TLI, and 3 months post-TLI WBC counts and SDs were 7.95±1.07, 4.72±0.36, and 5.94±1.52 thousand/mm³ (p=0.013), respectively. The mean pre-TLI, immediate post-TLI, and 3 months post-TLI azathioprine doses and SDs were 1.9±0.3, 1.3±0.2, and 1.1±0.7 mg/kg/d (p<0.0001), respectively.

Table 4 demonstrates the effect of TLI for acute intractable rejection in this group of six selected patients. The mean pre-TLI and post-TLI number of rejection episodes per 100 patient-days were 3.07 (range, 0.71 to 8.11) and 0.12 (range, 0.0 to 0.39), respectively (p=0.0043). The rejection-free interval was more than 15 months in four of the patients and more than 60 months in the two survivors after TLI. However, four of the five recipients surviving more than a year following TLI developed OB. The median time from transplantation to the development of OB was 353 days (range, 206 to 799 days). Patient 1 developed OB over a year prior to receiving TLI. Patients 4, 5, and 6 developed OB after receiving TLI.

There were a total of 23 ARs in the TLI group and 37 ARs in the rejector group. One recipient from the rejector group received pulsed MP for greater than grade 2 acute rejection more than twice and qualified for TLI as defined in the Materials and Methods section. This patient was not considered because of the development of a Pseudomonas aeruginosa lung abscess. The cumulative incidence of OB at 1, 2, and 3 years following transplantation for the TLI group was 33%, 56%, and 78%, respectively. The cumulative incidence of OB at 1, 2, and 3 years following transplantation for the rejector group was 10%, 33%, and 43%, and for the nonrejectors was 7%, 26%, and 39%, respectively. The patient not considered for TLI in the rejector group because of the lung abscess was diagnosed as having OB on postoperative day (POD) 231. Intergroup comparisons did not achieve statistical significance.

**Clinical Course**

Patient 2 developed ARDS and died shortly on completing TLI. It was not possible to determine if TLI contributed to the development of ARDS. The remaining five patients survived at least 1 year following TLI.

Patient 6 developed biopsy-proved OB 227 days after TLI on POD 434. Following an increase in her steroid dosage, she developed a nonspecific organizing pneumonia and respiratory failure requiring mechanical ventilation. TLI was reinstituted; however, this was interrupted upon the isolation of CMV from her blood. She underwent an open-lung biopsy; the biopsy specimen revealed chronic pulmonary vascular rejection and OB. This was complicated by a bronchopleural

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<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Interval to TLI, d</th>
<th>TLI Duration, d</th>
<th>TLI Dose Received, cGy</th>
<th>Complications</th>
<th>Post-TLI Period, d</th>
<th>Days Alive</th>
<th>Status</th>
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<tbody>
<tr>
<td>1</td>
<td>707</td>
<td>32</td>
<td>800</td>
<td>None</td>
<td>457</td>
<td>1,196</td>
<td>Dead</td>
</tr>
<tr>
<td>2</td>
<td>313</td>
<td>36</td>
<td>800</td>
<td>None</td>
<td>51</td>
<td>390</td>
<td>Dead</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>34</td>
<td>800</td>
<td>PCP*</td>
<td>1,937</td>
<td>2,006</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>42</td>
<td>800</td>
<td>None</td>
<td>679</td>
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<tr>
<td>5</td>
<td>108</td>
<td>31</td>
<td>800</td>
<td>None</td>
<td>1,740</td>
<td>1,879</td>
<td>Alive</td>
</tr>
<tr>
<td>6</td>
<td>176</td>
<td>31</td>
<td>800</td>
<td>None</td>
<td>372</td>
<td>579</td>
<td>Dead</td>
</tr>
</tbody>
</table>

*PCP=Pneumocystis carinii pneumonia.*

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**Table 2—Summary of Pre-TLI and Post-TLI Treatment**

**Table 3—The Effect of TLI and Azathioprine on the WBC Count**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Pre-TLI WBC</th>
<th>Azathioprine, mg/kg/d</th>
<th>Post-TLI WBC Count Immediately</th>
<th>Azathioprine, mg/kg/d</th>
<th>WBC Count 3 mo</th>
<th>Azathioprine, mg/kg/d</th>
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<tbody>
<tr>
<td>1</td>
<td>6.7</td>
<td>1.83</td>
<td>5.1</td>
<td>0.57</td>
<td>4.6</td>
<td>0.09</td>
</tr>
<tr>
<td>2</td>
<td>9.2</td>
<td>1.75</td>
<td>4.5</td>
<td>0.00</td>
<td>7.7</td>
<td>1.04</td>
</tr>
<tr>
<td>3</td>
<td>7.3</td>
<td>1.32</td>
<td>4.6</td>
<td>0.40</td>
<td>7.4</td>
<td>2.02</td>
</tr>
<tr>
<td>4</td>
<td>9.3</td>
<td>2.08</td>
<td>5.1</td>
<td>0.00</td>
<td>5.5</td>
<td>1.21</td>
</tr>
<tr>
<td>5</td>
<td>7.4</td>
<td>2.23</td>
<td>4.3</td>
<td>0.33</td>
<td>4.5</td>
<td>0.96</td>
</tr>
<tr>
<td>6</td>
<td>7.8</td>
<td>2.03</td>
<td></td>
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</tr>
</tbody>
</table>
resulting fistula resulting in a protracted ICU course and death on POD 579.

Patient 4 developed severe (grade 4) lung rejection 483 days after TLI on POD 609. She had a serum cyclosporine level of 19 ng/mL and received a pulse of IV MP. This initiated a series of complications, including bacterial pneumonia, respiratory failure, enterococcal bacteremia, and prolonged mechanical ventilatory support. She died on POD 799.

Patient 1 presented on POD 212 with severe lung rejection complicated by hypoxemic respiratory failure and mechanical ventilation. She responded to IV “pulsed” MP. However, she developed progressive airflow obstruction and was subsequently diagnosed as having OB on POD 273. Her condition stabilized with moderate airflow obstruction and she returned to college with minimal limitations. She later developed recurrent cardiac rejection complicated by mild congestive heart failure and received TLI for cardiac rejection on POD 707. Her condition improved and she returned to college. She developed hepatic failure due to hepatitis C acquired by blood transfusions on POD 212 and died on POD 1,196 of hepatorenal syndrome.

The remaining two patients are free of acute rejection more than 4 years following TLI. Patient 5 had an episode of CMV pneumonitis prior to her acute rejection episodes and following TLI developed mild reductions in her pulmonary function test results. A biopsy specimen confirmed OB on POD 206. Augmentation of her prednisone dosage stabilized her deteriorating lung function. She is currently working part time and using supplemental oxygen at night and with exertional activities. Patient 3 is working full time with no functional limitations. He had clinical rejection on POD 10 and grade 4 rejection by transbronchial lung biopsy on PODs 15 and 34 prior to receiving TLI.

**Discussion**

Radiotherapy for clinical transplantation was originally administered in the form of total body irradiation more than 3 decades ago to induce prolonged renal allograft acceptance. However, it was limited by unacceptable severe bone marrow and GI toxic reactions. The subsequent refinements in the fractionation, dose per fraction, total radiation dose, and mode of delivery minimized the total radiation exposure and targeted the therapy to the lymphatic system. These modifications in combination with the realization of the sustained impairment of cell-mediated immune reactivity directed further investigation into the potential use of TLI as an immunosuppressive agent in animal models, human autoimmune disease states, and clinical transplantation.

Slavin and associates at Stanford University first reported long-term skin allograft survival in mice following preoperative preparation with fractionated TLI. The regimen led to the development of skin, marrow, and heart allograft tolerance in a rat model. Additional investigations demonstrated that TLI in combination with low-dose cyclosporine therapy was synergistic and resulted in improved survival of rodent cardiac xenografts.

Large animal experiments established dosing regimens and confirmed the possibility of long-term allograft tolerance. The Stanford group achieved long-term canine heart allograft survival with preoperative TLI in combination with postoperative antithymocyte globulin and azathioprine. Myburgh et al used TLI alone and in combination with other agents in primate models of liver and kidney transplantation and observed graft tolerance in 30 to 50% of animals receiving only TLI.

Stanford researchers reported that patients cured of Hodgkin’s disease by radiation therapy had decreases in both number and function of peripheral blood T lymphocytes. It was shown that small lymphocytes were particularly vulnerable to genomic damage from IR resulting in cytolysis during mitosis. The incidence of infections exclusive of herpes zoster was reported to be less than 1%. Thirty percent of patients treated with TLI for Hodgkin’s disease developed herpes zoster with less than 10% of these patients requiring hospitalization. Moreover, the risk of secondary tumor development was not increased.

The proved clinical safety and potent immunosuppressive effect of TLI combined with encouraging re-

<table>
<thead>
<tr>
<th>Pre-TLI</th>
<th>Post-TLI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No.</td>
<td>Rejection Episodes/100 Patient-days</td>
</tr>
<tr>
<td>1</td>
<td>0.71</td>
</tr>
<tr>
<td>2</td>
<td>1.28</td>
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<tr>
<td>3</td>
<td>8.11</td>
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<td>4</td>
<td>3.85</td>
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<td>5</td>
<td>2.77</td>
</tr>
<tr>
<td>6</td>
<td>1.7</td>
</tr>
</tbody>
</table>
sults from animal studies prompted experimental use in human transplantation. Results from the University of Minnesota suggested that TLI might be a valuable adjunct in high-risk patients requiring retransplantation following failure of their initial renal allograft from rejection. Immunologic studies demonstrated a prolonged reduction in HIV helper (CD4+) cells with a rapid recovery of HIV suppressor (CD8+) cells and a pattern of specific unresponsiveness to donor cells, which persisted up to 18 months after kidney transplantation. Saper and colleagues indicated that adjuvant TLI might allow reduction of maintenance immunosuppression.

Kahn and colleagues reported favorable results in cardiac transplantation with the use of preoperative TLI combined with the administration of donor marrow and conventional immunosuppression in high-risk patients. Pretransplant TLI in combination with donor marrow transplantation was reported in six heart recipients. Two patients in this series were alive at 4 years, one died of heart failure at 10 days, two died of infection within 7 weeks, and one died of rejection at 7 months. Ancedotal reports have demonstrated that TLI reversed resistant rejection events in cardiac recipients. Hunt et al reported the first series of ten patients treated with TLI for intractable cardiac rejection. There was no serious morbidity or mortality due to TLI treatment and three patients had no further rejection episodes at follow-up ranging from 2.4 to 37.3 months. Salter et al demonstrated a striking reduction in acute cardiac rejection events before and after TLI with a reduced rejection frequency from 1.3 episodes per month to 0.07 episodes per month. They specifically analyzed a contemporaneous cohort of patients immediately before the TLI protocol who received identical baseline immunosuppression and generated a time-related rejection incidence in order to prove that the decrease in rejection following TLI did not merely follow the predicted decline in rejection frequency over time. Furthermore, they noted an increased incidence of infections during TLI which were all successfully treated. One patient died of severe cardiac rejection despite TLI, MP, and antithymocyte globulin. Evans et al reported successful TLI treatment in five of six adult cardiac transplant recipients. In four of these patients, CMV reactivation occurred during TLI therapy but was successfully treated.

We report for the first time (to our knowledge) the use of TLI in HLT and LT. The results demonstrate that TLI is well tolerated in heart-lung and lung allograft recipients, and it can reverse the morphologic changes in those patients with intractable rejection. There were no life-threatening complications attributable to TLI, although one patient developed ARDS within weeks after TLI.

TLI effectively reduced the number and severity of rejection episodes in this group of patients who had already received high-dose MP for more than two episodes of AR. In addition, TLI may have conferred some long-term protection against cellular rejection as exemplified by two patients who have had no AR episodes since TLI. However, TLI did not alter the development of OB. This is in contrast to the lower cumulative incidence of OB seen in the contemporaneous cohorts, particularly the nonrejector group who remains free from acute rejection. The cumulative incidence of OB among the three groups was not significantly different; however, this could result from too few numbers in the TLI group. The higher cumulative incidence of OB in the TLI group may be anticipated as a result of the frequency and intensity of ARs.

In contrast to data from Saper and associates, TLI did not allow tapering of the other immunosuppressive drug dosages because severe rejection developed in conjunction with documented low levels of cyclosporine following TLI in this and another series. The utilization of TLI in this series may have selected out aggressive immune responders or those who may be relatively resistant to conventional immunosuppression. Thus, the dose of TLI was used as an adjunct to reverse intractable rejection.

This low-dose TLI with its immunosuppressive effect resulted in leukopenia necessitating adjustments in the azathioprine dose. However, there were no life-threatening infectious complications in the heart-lung and lung recipients or any of the previously reported heart recipients. The development of viral infections appears to be the most common adverse effect of low-dose TLI in clinical transplantation. There were two deaths related to disseminated herpes simplex and CMV pneumonitis in the report from Levin et al, however, up to 2,000 cGy of radiation therapy was used in those patients. To our knowledge, there have been no cases of posttransplant lymphoproliferative disorder reported in those patients who received less 2,000 cGy, including this series.

Whether administering more MP or a steroid-sparing modality to minimize the side effects of steroid therapy in managing these “severe rejectors” is unknown. The steroid-sparing options include methotrexate, cyclophosphamide, monoclonal or polyclonal anti-T-cell antibodies, and TLI. The small numbers of patients in this investigation and the lack of randomizing TLI with any other modalities for-recalcitrant acute rejection are the major limitations of this report. However, TLI appears to have merit for consideration for a select group of lung allograft recipients who have repeatedly received large amounts of MP for recurrent or intractable AR.

In summary, this series provides the basis for further
investigational use of TLI as a potent immunosuppressant in LT. The long-term effects of TLI in combination with conventional immunosuppression remain to be elucidated. Further exploration should address the use of TLI as salvage therapy in patients with recalcitrant acute rejection and its potential as adjuvant therapy for patients with chronic progressive deterioration of airway function from OB.

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