The Role of Photopheresis in the Treatment of Bronchiolitis Obliterans Syndrome

Selim M. Arcasoy, M.D.
Medical Program Director
Lung Transplantation Program
New York-Presbyterian Hospital
Columbia University Medical Center
New York, NY
Terminology/Definitions

- OB=BO: Obliterative bronchiolitis or bronchiolitis obliterans
  - Histopathologic term used to describe the finding of fibrous obliteration of small airways after LTx

- BOS: Bronchiolitis obliterans syndrome
  - Clinical/physiologic definition of chronic lung allograft dysfunction caused by OB and characterized by progressive airflow limitation
  - Term originally proposed in 1993 and revised in 2002
Bronchiolitis Obliterans Syndrome

Clinical Impact

Very common and deadly

• Cumulative risk of 50-80% between 5 and 10 years after lung transplantation

• Leading cause of long-term mortality
  • Directly or indirectly accounts for at least 30 to 50% of deaths after third post-operative year
  • Less than 40% survival at 5 years after its onset
Pathogenesis of OB

Injury to airway epithelium
Alloimmune or non-alloimmune
(rejection, infection, aspiration, ischemia)

Innate and adaptive immune response
(PMN, macrophage, DC, T- and B-lymphocytes)
IL-1, IL-2, IL-6, IL-8, IL-12,
TNF-α, MCP-1, complement,
IFN-γ, RANTES, ROS, NO,
peroxides, leukotrienes

Inflammatory response
Vascular changes

Final common pathway
Repair response
Fibroblast proliferation
EC matrix deposition

TGF-β, PDGF,
IGF, FGF, ET-1

Normal
Mechanisms and Therapy of OB After Lung Tx
Adapted from Nicod. Proc Am Thorac Soc 2006;3:444

Irritants/ Pollutants
GER, smoke

Innate immunity
Autoimmunity
Inflammation

Infections
CMV
CARV

Adaptive immunity
Dendritic cell activation
Cytotoxic cell activation

Increased alloantigen expression
HLA-A, B, DR

Immunosuppression
Immunomodulation

Steroids

Inflammatory Cytokines

Acute rejection
Acute injury

Active OB
Inactive OB
## Prevention and Treatment of BOS

### Potential Therapies

- Induction therapy
- Tacrolimus
- Mycophenolate mofetil
- Everolimus
- Aerosol Cyclosporine
- Azithromycin
- Antireflux procedures for GER
- Statins

- Extracorporeal photopheresis
- Lympholytic therapy
- Total lymphoid irradiation
- Donor bone marrow tx
- Cyclophosphamide
- Methotrexate
- Preservation of airway microcirculation
Potential Mechanisms of ECP

- Induction of T-cell apoptosis
  - Only 5% of lymphocyte load is treated with each cycle of ECP
- Induction of immunologic tolerance rather than immunosuppression
  - No altered T- and B-cell function in patients after ECP
  - Acquisition of a tolerogenic phenotype by immature dendritic cells
  - Increase in regulatory T-cells
- Conflicting effects on cytokine production
- “T-cell vaccination”
  - Th1 immune response against alloreactive T cells
ECP Process

- Removal of a certain percentage of a patient’s blood (2-5% of total circulating leukocytes)
- Separation of blood into leukocyte-enriched (buffy coat) and -depleted components
- Buffy coat is exposed to UV light in the presence of 8-methoxypsoralen within the photoactivation chamber, which forms covalent bonds to DNA pyrimidine bases, cell surface and cytoplasmic components of exposed leukocytes
- Leukocyte apoptosis, changes in dendritic cells, cytokine production and induction of Tregs
ECP History in Lung Transplantation

• First report in 3 lung transplant patients with BOS published in 1995

• Initially used in the context of refractory BOS (stages 2-3) with demonstration of initial stabilization or improvement in FEV$_1$

• Literature suggested its efficacy in persistent acute rejection and early BOS, preventing further loss of lung function

• 2 recent larger studies suggested reduction in the rate of decline in lung function at all stages of BOS
Extracorporeal Photopheresis
Early Clinical Studies in Lung Transplantation

- Case series including 3-14 patients
  - Slovis. *NEJM* 1995;332:962—(n=3)
  - Salerno. *JTCS* 1999;117:1063—(n=8)

- Reduced rate of decline in FEV₁ in most patients
  - More likely to be effective in earlier stages of BOS but stabilization of lung function observed in stage 3 BOS
ECP. A 10-year Single Center Experience
Benden et al. Transplantation 2008; 86:1625

- 24 patients underwent ECP between 1997-2007
- 12 cycles 4-6 weeks apart
- BOS grades
  - Stage 1 N=5
  - Stage 2 N=2
  - Stage 3 N=5

<table>
<thead>
<tr>
<th>TABLE 1. Patient demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
</tr>
<tr>
<td>Male/female</td>
</tr>
<tr>
<td>Mean age at transplant (SD), (yrs)</td>
</tr>
<tr>
<td>Diagnosis at transplant</td>
</tr>
<tr>
<td>CF (%)</td>
</tr>
<tr>
<td>COPD (%)</td>
</tr>
<tr>
<td>IPF (%)</td>
</tr>
<tr>
<td>PAH (%)</td>
</tr>
<tr>
<td>Type of transplant</td>
</tr>
<tr>
<td>Double lung (%)</td>
</tr>
<tr>
<td>Single lung (%)</td>
</tr>
<tr>
<td>Indication for ECP</td>
</tr>
<tr>
<td>BOS (%)</td>
</tr>
<tr>
<td>Recurrent AR (%)</td>
</tr>
<tr>
<td>Mean baseline FEV$_1$ posttransplant (SD), (L)</td>
</tr>
</tbody>
</table>

CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; PAH, pulmonary arterial hypertension; ECP, extracorporeal photopheresis; BOS, bronchiolitis obliterans syndrome; AR, acute rejection; FEV$_1$, forced expiratory volume in 1 sec.
Decline in FEV1
Pre ECP 112 ml/mo
Post ECP 12 ml/mo
Mean change (95% CI) 100 (28-171) ml
P=0.011
ECP. A 10-year Single Center Experience

*Benden et al. Transplantation 2008; 86:1625*

- ECP for recurrent acute rejection in 12 patients
- \( \geq 2 \) biopsy proven episodes of acute rejection (\( \geq \) grade A2)
  - All except one had follow-up biopsy during ECP
  - Only 2 patients had an episode of \( \geq \) grade A2 rejection
  - None developed BOS with clinical stabilization
- No adverse effects
- Median survival from LTx 7 yrs, from ECP 4.9 yrs
The Efficacy of Photopheresis for BOS

Morrell. JHLT 2010;29:424

- 60 patients with BOS between Jan 2000-Dec 2007
  - 34 early- (within 2 years) and 26 late-onset BOS

- Primary endpoint: rate of change in lung function before and after initiation or ECP

- BOS stage prior to ECP
  - Stage I: 8.3%, II: 33.3% and III: 58.3%

- ECP schedule (cycle=2 days)
  - 5 cycles first month, 4 cycles in next 2 months and 3 cycles next 3 months to complete 6 months
Absolute FEV$_1$ Pre- and Post-ECP Slope of Linear Regression Line
## Patient Demographics

*Morrell. JHLT 2010;29:424*

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Result No (%) or Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>60 (100)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 (21-72)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>32 (53)</td>
</tr>
<tr>
<td>Pretransplant diagnosis</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>26 (43)</td>
</tr>
<tr>
<td>CF</td>
<td>11 (18)</td>
</tr>
<tr>
<td>IPF</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Type of Ltx (Bilateral)</td>
<td>57 (95)</td>
</tr>
<tr>
<td>BOS stage</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>2</td>
<td>20 (33.3)</td>
</tr>
<tr>
<td>3</td>
<td>35 (58.3)</td>
</tr>
<tr>
<td>Prior ATG treatment</td>
<td>58 (96.7)</td>
</tr>
</tbody>
</table>
Results (I)

Morrell. JHLT 2010;29:424

• 6-month pre and post-ECP treatment
  • Pre-ECP mean rate of decline in FEV$_1$ -116 ml/mo
  • Post-ECP mean rate of decline in FEV$_1$ -28.9 ml/mo
  • Mean difference in rate of decline 87.1 ml/mo (95% CI 57.3-116.9 ml/mo, p<0.0001)
  • Decline in FEV$_1$ in a 6-month period 696 ml vs 173 ml

• When FEV$_1$ was entered as 0 in patients who died after initiation of ECP, mean difference in rate of decline was still significant (58.7 ml/mo, p=0.003)

• When 5 BOS stage I patients were excluded, mean difference in rate of decline remained significant
Change in Rate of Decline in FEV$_1$
Results (II)

*Morrell. JHLT 2010;29:424*

- Rate of decline was reduced after initiation of ECP in 44 patients (79%)
  - 14 (35%) of these patients had an improvement in FEV₁ with an increase above pre-ECP values
  - Mean rate of increase in these patients was 20.1 ml/mo and mean gain in lung function in 6 mo was 120.6 ml

- Clinical characteristics were not predictive

- 12-month efficacy in the mean rate of FEV₁ decline
  - -21.4 ml/mo and decline of 128.4 ml in 12 month period
  - Mean difference pre and post-ECP 94.6 ml/mo (p<0.0001)
Rate of Decline in FEV₁ Pre-ECP, 6 months and 12 months Post-ECP
Safety and Tolerability

- 10 of 60 patients had complications
- 8 (13%) with indwelling catheter related bacteremia
- 1 with partially occlusive thrombus in SVC
- 1 with transient hypotension during ECP
- No malignancies
**Guidelines On The Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach**

*Apheresis Applications Committee of the American Society for Apheresis*

<table>
<thead>
<tr>
<th>Disease</th>
<th>Modality</th>
<th>Category</th>
<th>Recommendation Grade</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Allograft rejection</td>
<td>ECP</td>
<td>2</td>
<td>1C</td>
<td>126</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Refs 173, 174, 400-412</td>
</tr>
</tbody>
</table>

**Category 2:** Disorders for which apheresis is accepted as a second-line therapy, either as a standalone treatment or in conjunction with other modes of therapy

**Recommendation Grade:** Strong recommendation, low quality evidence; from observational studies or case series

**Implications:** Strong recommendation but may change when higher quality evidence becomes available

*J Clin Apheresis 2010;25:83-177*
Extracorporeal Photopheresis (ECP)

- Autoimmune diseases
  - Scleroderma: Category 4, grade 1A
- Graft versus host disease (skin vs non-skin)
  - Category 2 and 3; grade 1B and 2C
- Cutaneous T-cell lymphoma (erythrodermic versus non-erythrodermic)
  - Category 1 and 3, grade 1B and 2C
- Prophylaxis and treatment of heart transplant rejection
  - Category 1 and 2, grade 1A and 1B
- Lung transplant rejection
  - Category 2, grade 1C
Guidelines On The Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach

Apheresis Applications Committee of the American Society for Apheresis

• Frequency
  • Variable: Biweekly to every 2 weeks, larger intervals of every 4-6 weeks reported
  • Generally weekly cycles for 4-6 wks, then every other week for 6 weeks followed by monthly cycles

• Duration and discontinuation
  • Optimal duration unknown
  • Number of treatment cycles varied between 6-24
  • Long-term continuation may be necessary in responders
Conclusions

- BOS is the single most important cause of limited long-term survival after lung transplantation
- There are limited treatment options for BOS, none of which have been approved
- Photopheresis is one treatment option for BOS, which has been shown to result in preservation of lung function with low side-effect profile
  - Accepted as second-line therapy and recommended strongly by the American Society of Apheresis
  - ECP should be made available for patients with BOS