APHERESIS FOR DESENSITIZATION OF NON-RENAL TRANSPLANTS

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OVERVIEW

- Immunologic barriers to solid organ transplantation
  - ABO incompatibility
  - HLA antigen system
    - Sensitization terminology
- Why non-renal transplants
- The clinical problem:
  - Sensitization and wait times
  - Graft outcomes
- Desensitization protocols
- Duke Experience
IMMUNE BARRIERS TO TRANSPLANTATION

- ABO system
- HLA system
ABO ANTIGENIC SYSTEM

Type A

Type B

Type AB

Type O
HLA SYSTEM

- HLA glycoproteins on surface of all cells in body
- Function: recognition molecules in initiation of immune responses
- Two classes:
  - HLA class I (HLA A, -B and -C); expressed on all nucleated cells
  - HLA class II (HLA DR, -DQ and –DP)
    - On APCs, B lymphocytes, activated T cells and microvascular endothelial cells
HLA Abs are not naturally occurring: transfusion, prior transplantation or pregnancy
Degree of sensitization:

- % PRA: % of a panel of individuals of various HLA phenotypes to whom a patient is reactive
- Calculated PRA: % of potential donor population bearing antigens to which a patient has Abs

Highly sensitized: >80% PRA
THE CLINICAL PROBLEM

- Sensitization rates:
  - 30% of renal transplant
  - 10-15% of lung transplants
  - 11% of heart transplant

- How it impacts transplant population:
  - Increased wait times
  - Graft dysfunction/mortality

**CLINICAL PROBLEM**

*Fig. 1.* Median heart transplant waiting time, stratified by sensitized (PRA > 10%) or non-sensitized (PRA < 10%) status.

*Eckman et. al., Clin Transplant 2010;24:726-734.*
HLA SENSITIZATION

- Hyper acute or acute rejection
- Heart transplant patients\(^1\):
  - Decreased survival
  - Increased rejection
  - Increased cardiac allograft vasculopathy
- Lung transplantation\(^2\)
  - Persistent rejection
  - Increased bronchiolitis obliterans
  - Worsened survival

Patients with PRA>25%:
- Higher rejection rate 1 yrs
- Worse allograft survival
- Worse mortality

Ann Thorac Surg 2007; 84: 1556-63
LUNG TRANSPLANT SURVIVAL: HLA SENSITIZATION

10,000 patients from 1987-2005

Survival (%) vs Time (Years)

<table>
<thead>
<tr>
<th>PRA%</th>
<th>30 DAYS</th>
<th>1 YR</th>
<th>3 YRS</th>
<th>5 YRS</th>
<th>p-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (8488)</td>
<td>91.9% (7753)</td>
<td>77.7% (6299)</td>
<td>61.1% (3846)</td>
<td>47.7% (2186)</td>
<td>0.005</td>
</tr>
<tr>
<td>1-10 (1259)</td>
<td>91.8% (1145)</td>
<td>78% (939)</td>
<td>60% (580)</td>
<td>44.8% (334)</td>
<td>0.64</td>
</tr>
<tr>
<td>11-25 (249)</td>
<td>90.3% (224)</td>
<td>73.3% (177)</td>
<td>56.3% (105)</td>
<td>43.7% (64)</td>
<td>0.13</td>
</tr>
<tr>
<td>&gt;25 (240)</td>
<td>84.1% (200)</td>
<td>69.3% (149)</td>
<td>50.3% (84)</td>
<td>40.1% (44)</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

SUMMARY: HLA ANTIGENS & ANTIBODIES

- Good to have your own HLA antigens, but not others
- HLA sensitization is a problem
- HLA antibodies
  - Longer wait times to receive organs
  - Worse survival
  - Worse graft function (BOS) and survival
- What can be done about this?
DESENSITIZATION

Desensitization = Antibody reduction therapy
Why Focus on Non-Renal Transplants?

- Renal transplants
  - Cadaveric
  - Living-related donors
- HLA sensitized individuals
  - Robust literature with prospective clinical trials
  - Basis for transplant approaches in other organs
  - Desensitization protocols can be timed to organ transplantation
- Other organs: no living related donor options available
### Renal Transplantation

<table>
<thead>
<tr>
<th>Incidence: 6 per 100,000/year in the US; AMR 10% renal transplant recipients and 40% renal transplant recipients who underwent desensitization</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPE</td>
<td>Grade 1B</td>
<td>I (AMR)</td>
<td></td>
</tr>
<tr>
<td>TPE</td>
<td>Grade 1B</td>
<td>II (Desensitization, living donor, positive crossmatch due to donor specific HLA antibody)</td>
<td></td>
</tr>
<tr>
<td>TPE</td>
<td>Grade 2C</td>
<td>III (High PRA, cadaveric donor)</td>
<td></td>
</tr>
</tbody>
</table>

For desensitization protocols, TPE is performed daily or every other day per protocol until crossmatch becomes negative. TPE is also performed post-operatively for a minimum of 3 procedures. Further treatment is determined by risk of AMR, DSA titers, or the occurrence of AMR.

### Lung Allograft Rejection

<table>
<thead>
<tr>
<th>Incidence: Chronic rejection: 28% at 2 years, 50% at 5 years, and 74% at 10 years</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECP</td>
<td>Grade 1C</td>
<td>II</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th># of reported patients*: 100–300</th>
<th><strong>Type of evidence</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>CT</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Cardiac Allograft Rejection

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ECP</td>
<td>Grade 1A</td>
<td>I (prophylaxis)</td>
<td></td>
</tr>
<tr>
<td>ECP</td>
<td>Grade 1B</td>
<td>II (treatment of cellular rejection)</td>
<td></td>
</tr>
<tr>
<td>TPE</td>
<td>Grade 2C</td>
<td>III (treatment of AMR)</td>
<td></td>
</tr>
</tbody>
</table>
PROS & CONS OF DENSENSTIZATION

**Pro:**
- Increase access to transplantation
- Improve graft viability/function
- Prolong life

**Con:**
- Patient safety/outcomes
- Allograft function
- Financial burden
- Timing (LRD not an option for lung/heart/liver)
- Heterogeneity of studies (no standard protocols)
PROTOCOLS FOR DESENSITIZATION

- Aim: decrease level of antibodies, and maintain it low/negative
  - Pre or post transplant antibody removal
  - Removal of antibodies prior to transplantation (desensitization)
  - Treatment of antibody mediated rejection (AMR)

- No protocols approved by FDA for the moment
  - No standardization

- Renal transplant data is most robust
DESENSITIZATION PROTOCOLS

- High dose IVIG
- Plasmapheresis + low dose IVIG
- Additional agents:
  - Medications: FK506, MMF, steroids
  - Antibodies: Daclizumab (α-CD25/IL-2R), basiliximab (α-CD25/IL-2R), alemtuzumab (α-CD52), rituximab (α-CD20), eculizumab (α-C5)
  - Chemotherapy: bortezomib
DESENSITIZATION PROTOCOLS
### Table 2. Examples of Desensitization Therapies

<table>
<thead>
<tr>
<th></th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmapheresis</td>
<td>(A) 1.5 volume exchanges</td>
<td>(A) 5 consecutive days</td>
</tr>
<tr>
<td></td>
<td>(B) 5 times, every other day</td>
<td>(B) 5 times, every other day</td>
</tr>
<tr>
<td></td>
<td>(C) 2–3 times/week until transplant</td>
<td>(C) 2–3 times/week until transplant</td>
</tr>
<tr>
<td></td>
<td>(D) 5 times, every other day, every 2–4 weeks</td>
<td>(D) 5 times, every other day, every 2–4 weeks</td>
</tr>
<tr>
<td>Intravenous immunoglobulin (IVg)</td>
<td>(F) 1.5 volume exchanges</td>
<td>(A) Every 2–4 weeks</td>
</tr>
<tr>
<td></td>
<td>(A, B) 2 g/kg IV divided over 2 days</td>
<td>(B) Every 2–4 weeks</td>
</tr>
<tr>
<td></td>
<td>(C) 2–3 g/kg IV divided over 4 days</td>
<td>(C) Every 2–4 weeks</td>
</tr>
<tr>
<td></td>
<td>(D) 0.1 mg/kg IV</td>
<td>(D) Every 2–4 weeks</td>
</tr>
<tr>
<td></td>
<td>(E) 100 mg/kg IV</td>
<td>(E) Every 4 weeks</td>
</tr>
<tr>
<td></td>
<td>(F) 20 g (of 10% IVg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(G) 150 g (of 10% IVg) divided over 3 rounds</td>
<td>(G) Every 2 weeks</td>
</tr>
<tr>
<td>Rituximab</td>
<td>(A) 1 g IV</td>
<td>(A) Weekly times 4</td>
</tr>
<tr>
<td></td>
<td>(C) and (E) 375 mg/m²</td>
<td>(C) Times 2 doses</td>
</tr>
<tr>
<td></td>
<td>(G) 500 mg</td>
<td>(E) Weekly times 4</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>(A) 1 mg/kg orally</td>
<td>(G) Every 2 weeks</td>
</tr>
<tr>
<td>(used in the past)</td>
<td>(C) 0.5–1 g/m² IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(D) 1 mg/kg orally</td>
<td>(A) Daily</td>
</tr>
</tbody>
</table>

(A) = UCLA; (B) = Stanford University; (C) = University of Maryland; (D) = University of Toronto; (E) = University of Wisconsin; (F) = Loyola Medical Center; (G) = University of Berlin. IV, intravenous.
ADULT HEART TRANSPLANT

- N=6 heavily sensitized patients awaiting heart transplant
  - cPRAs >50% (MFI threshold >5000)
  - Mean PRA : 51-88% (mean cPRA =62%)
- Bortezomib given D1, 4, 7 and 10
  - PLEX given for 2 days prior to bortezomib (8 times)
  - HLA antibodies determined 1-2 weeks after desensitization protocol
- Follow up of cPRA : decrease from 62% to 35%
- 4/6 transplanted successfully
- 2/6 patients died from sepsis complications

Patel et. Al. J Heart Lung Transplant, 2011: 30
### Table 2: White Blood Count (WBC) Trend and Adverse Events With Bortezomib Therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Number of bortezomib doses</th>
<th>WBC prior to bortezomib (103/µL)</th>
<th>Lowest WBC during bortezomib therapy (10³/µL)</th>
<th>Infection</th>
<th>Neuropathy</th>
<th>Bortezomib dose adjustment (reason)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>11.4</td>
<td>5.5</td>
<td>BiVAD drive-line infection, <em>Candida tropicalis</em></td>
<td>Yes (mild)</td>
<td>Yes (neuropathy)</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>7.8</td>
<td>6.4</td>
<td>Catheter tip CNS, <em>Klebsiella UTI</em></td>
<td>No</td>
<td>Yes (anemia)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>7.5</td>
<td>3.7</td>
<td>Sputum <em>Candida parapsilosis</em>, urine <em>Candida glabrata</em>, <em>Escherichia coli UTI</em></td>
<td>Yes (mild)</td>
<td>Yes (neuropathy)</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>8.4</td>
<td>6.1</td>
<td>Catheter tip CNS, <em>C diff stool</em></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>5.5</td>
<td>3.3</td>
<td>None</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>4.2</td>
<td>2.8</td>
<td>CNS bacteremia</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>6.6</td>
<td>6.4</td>
<td><em>C diff stool</em></td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*CNS, coagulase-negative *Staphylococcus aureus*; *C diff, Clostridium difficile; UTI, urinary tract infection.*

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No mention of immunoglobulin levels post transplant

*Patel et. Al. J Heart Lung Transplant, 2011: 30*
### TABLE 1  Peritransplant desensitization regimen for lung transplant recipients sensitized to third-party HLA antigens

<table>
<thead>
<tr>
<th>Time</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>At transplant</td>
<td>IVIG (2g/kg) + ECI</td>
</tr>
<tr>
<td>Posttransplant week 1</td>
<td>IVIG (500mg/kg) + daily ECI</td>
</tr>
<tr>
<td>Posttransplant weeks 2–4</td>
<td>IVIG (500mg/kg) + weekly ECI</td>
</tr>
<tr>
<td>Posttransplant weeks 5–24</td>
<td>IVIG taper</td>
</tr>
</tbody>
</table>

N=12 patients desensitized  
N=23 who did not
LUNG DESENSITIZATION

- 6/7 patients cleared Class I Abs (mean = 83 days)
- 1/3 cleared Class II antibodies cleared

Appel et. Al. Human Immunology 2005
DUKE EXPERIENCE
DUKE TRANSPLANT VOLUMES

Year
# procedures
6% 5%
9%
16%
22%
24%

Organ/Indication
Heart Lung Renal GI
# procedures
Total Desensitization
23%
68%
7%
The study was approved through the Duke University IRB (IRB#00044155).

Candidates with cPRA>80% were eligible.

Study period 2010-2013

**HLA antibody determination and screening**

- Flow cytometry screening with panel reactive antigen (PRA) beads and single antigen beads (Luminex, One Lambda) MFI=1000.
- A repeat sample to confirm all de novo HLA antibodies.
- HLA antibody tests pretransplant at all clinic visits (typically every 1-3 months) and then monthly while on the transplant waiting list.
DUKE’S CURRENT PROTOCOL

Duke’s actual protocol of pre TX desensitization

Apheresis

IV Ig
0.5g/kg

ITUXIMAB

TORVETOMAB

Induction treatment
Basiliximab, methylprednisolone, IVIg

Tacrolimus
MMF
Prednisone

Maintenance treatment

Transplantation

Until Tx

Flechner et. Al. Transplantation 2010
### DUKE DESENSITIZATION PROTOCOL: RESULTS

**Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Pretransplant sensitized (n=236)</th>
<th>Pretransplant sensitized + multimodal therapy (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, female, n (%)</td>
<td>122 (52)</td>
<td>13 (72)</td>
<td>0.09</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>208 (88)</td>
<td>14 (78)</td>
<td>0.23</td>
</tr>
<tr>
<td>Black</td>
<td>24 (10)</td>
<td>3 (17)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (2)</td>
<td>5 (5)</td>
<td></td>
</tr>
<tr>
<td>Native Lung Disease, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic</td>
<td>30 (13)</td>
<td>1 (11)</td>
<td>0.92</td>
</tr>
<tr>
<td>Obstructive</td>
<td>77 (33)</td>
<td>4 (44)</td>
<td></td>
</tr>
<tr>
<td>Restrictive</td>
<td>119 (50)</td>
<td>4 (44)</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>9 (4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Subsequent transplant, n (%)</td>
<td></td>
<td>9 (50)</td>
<td></td>
</tr>
<tr>
<td>Received complete therapy , n (%)</td>
<td></td>
<td>8 (44%)</td>
<td></td>
</tr>
</tbody>
</table>

*Snyder et. Al. Am J Respir Crit Care Med 187;2013:A2202*
## REASONS FOR INCOMPLETE PROTOCOL

8 of 18 patients completed full treatment course

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplanted</td>
<td>3</td>
</tr>
<tr>
<td>Initial patient, limited protocol</td>
<td>1</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia with bleeding concerns</td>
<td>4</td>
</tr>
<tr>
<td>Transplant ineligibility</td>
<td>1</td>
</tr>
</tbody>
</table>

_Snyder et. Al. Am J Respir Crit Care Med 187;2013:A2202_
CLASS I LEVELS INCREASED

- Class I percentage antibodies increased over time with the intervention (p=0.02 if partial protocol and p=0.009 if complete protocol).
- Estimated increase of 0.035 per day post therapy.

No change in Class II levels

*Snyder et. Al. Am J Respir Crit Care Med 187;2013:A2202*
DUKE: UNADJUSTED SURVIVAL

Blue= no multimodal therapy
Red= received multimodal therapy
P= by log rank

Transplant
9 of 18 candidates have been transplanted
2 of 18 candidates currently listed

Snyder et. Al. Am J Respir Crit Care Med 187;2013:A2202
STUDY CONCLUSIONS

- Multimodal therapy: small increase in PRA percentages for class I, though the clinical significance of this effect is unclear.
- No impact on cPRA.
- Posttransplant survival in our cohort was not statistically different than our larger cohort of pretransplant sensitized lung transplant recipients.
- Toxicities remain a problem

Snyder et. Al. Am J Respir Crit Care Med 187;2013:A2202
CONCLUSIONS

- Apheresis is a cornerstone for desensitization approaches
  - Needs to be partnered with multiple modalities
- Literature: arbitrary approaches to HLA desensitization
- Desperate need for standardization
  - cooperative groups
  - multi-center clinical trials
- Efficacy must be balanced by safety endpoints
  - Immunoglobulin levels (pre and post)
  - Coagulation studies (pre and post)
THANK YOU--