Immunologic Risk Factors: Approach to the Sensitized Patient

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Conflict of Interest Disclosure

- Alexion Pharmaceuticals – Research Grant
- I will discuss off-label use of the following drugs:
  - Rituximab, bortezomib, IVIG, eculizumab
The Challenge of the Sensitized Patient..

• Pre-transplant
  – Limited donor pool
  – Prolonged (prohibitive) time on wait-list
  – Increased wait-list mortality

• ...And yet the sensitized patient does not qualify for priority on the current (or proposed!) donor heart allocation scheme

2013 OPTN/SRTR Annual Report (All Organs)
Sensitization – an emerging problem

**Adult Heart Transplants**
**PRA Distribution**
(Transplants: January 2006 – June 2012)

- 66.3%
- 33.7%
- 15%
- 18.7%

If Class I and Class II values were reported separately, the higher of the two values was used.

**Graph:**
- 2002-2010 OPTN/SRTR Annual Report - Heart
Risk Factors for Sensitization

- Blood transfusion
- Infection
- Prior transplant
- Gender
- Race
- Prior cardiac surgery with homograft
- Ventricular Assist Devices

2004 OPTN/SRTR Annual Report
Pre-transplant Protocol: Management of Sensitized Patients – Heart

- Check PRA
  - < 10%
    - Recheck
      - q6m
      - 2w post sensitizing event
        - Infection
        - Transfusion
  - > 10%
    - Specification (Anti-HLA Ab)
    - Quantification (MFI)
    - ?c1q
    - Calculated PRA
      - <50%
        - Virtual Crossmatch
        - List for Transplant
      - >50%
        - Desensitization
          - Induction (rATG)
          - ± Plasmapheresis
          - ± IVig
          - ?Eculizumab
          - Post-Transplant Monitoring
            - Retrospective XM
            - Quantitative Abs (DSA)
            - Surveillance biopsies
            - Echocardiogram

Patel and Kobashigawa
## Desensitization Therapies

### Combined Strategies

<table>
<thead>
<tr>
<th>Approaches</th>
<th>Therapies</th>
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<tbody>
<tr>
<td>Antibody removal</td>
<td>Therapeutic Plasma Exchange, Immunoadsorption</td>
</tr>
<tr>
<td>To alter antibody production</td>
<td></td>
</tr>
<tr>
<td>B cell modulation</td>
<td>Rituximab, Bortezomib</td>
</tr>
<tr>
<td>Plasma cell depletion</td>
<td></td>
</tr>
<tr>
<td>Immunomodulation</td>
<td>IVIG</td>
</tr>
<tr>
<td>(Ab inactivation)</td>
<td></td>
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<tr>
<td>Suppression of the T-cell response</td>
<td>Steroids, cytolytic therapy, MMF, CNI</td>
</tr>
<tr>
<td>Complement blockade</td>
<td>Eculizumab</td>
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</tbody>
</table>
Desensitization in Heart Transplantation

Individual reductions in mean PRA levels of treated sensitized heart transplant candidates.

Treatments: plasma exchange, IVIg, rituximab

1-year Freedom From Any Treated Rejection

5-year Survival

Bortezomib

Proteasome inhibitor active against plasma cells

Normal breakdown of proteins

Bortezomib blocks the proteasome, causing an imbalance of proteins in the cells

Protein imbalance can lead to cell death
Refractory Antibodies in Heart Transplantation:

- cPRA ≥ 50% after IV Ig/ritux protocol
- Days 1, 4, 7, 10
- Plasma exchange
- Bortezomib 1.3 mg/m²
- Day 24
- Check PRA

Repeat 2-wk cycle if cPRA ≥ 50%

Desensitization with Plasma Exchange and Bortezomib for Refractory Antibodies:

N=7

Late Response to Desensitization Therapy

Efficacy of Desensitization
(Mean cPRA %)

N=9

Kobashigawa et al ATC 2012
Desensitization for Heart Transplantation with Plasma Exchange and Bortezomib

- 29 patients treated with plasma exchange and bortezomib
- 7 patients received prior therapies
  - Plasmapheresis
  - IVIg
  - Rituximab
- Overall modest decrease in cPRA
  - Mean cPRA 82% → 71%
- Bimodal response
  - 8/29 patients >15% drop in cPRA
  - For these patients:
    - Mean cPRA 79% → 45%

N=29

Patel J et al. ISHLT 2015
Desensitization for Heart Transplantation with Plasma Exchange and Bortezomib

N=29

Class I PRA

Class II PRA

Patel J et al. ISHLT 2015
Desensitization for Heart Transplantation with Plasmapheresis and Bortezomib

- All 29 patients successfully transplanted
- 1 death at 20 months at retransplant
- 10/29 (34%) treated for rejection
  - 3 patients ≥ ACR 2R
  - 3 patients ≥ AMR 2
  - 1 patient Biopsy Negative Rejection
  - 3 patients Mixed Rejection

Patel J et al. ISHLT 2015
Eculizumab

Antigen Antibody → C1 complex → C2a & C4b fragments → Classical pathway

→ C3 convertase → C3 hydrolysis → C3b and C3a fragments

Eculizumab → C3b cleaves C5 into C5a and C5b Anaphylotoxin

Cell swells and bursts → C5b, C6, C7, C8 and C9 together form the membrane attack complex
Eculizumab In Highly Sensitized Patients After Heart Transplantation
-DUET Pilot Study
clinicaltrials.gov NCT02013037

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Pilot Study of Eculizumab in Highly Sensitized Patients Undergoing Heart Transplant

• Pilot study using eculizumab immediately after heart transplant for the highly sensitized patient (PRA>70%).

• Study endpoints:
  – Assess efficacy to prevent symptomatic AMR or ACR.
  – IVUS to assess efficacy to prevent cardiac allograft vasculopathy (CAV).

• Eculizumab Protocol:
  – Eculizumab
    • Day 0: 1200 mg
    • Day 1,7,14,21: 900 mg
    • Day 28,42,56: 1200 mg
  – Thymoglobulin 1.5 mg/kg x 5days followed by IVIg 1 gm/kg x 2days

Patel/Kobashigawa – Cedars-Sinai DUET Study
<table>
<thead>
<tr>
<th>Demographics (N=10)</th>
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<tbody>
<tr>
<td>Mean recipient Age, Year ± SD</td>
</tr>
<tr>
<td>Mean Donor Age, Years ± SD</td>
</tr>
<tr>
<td>BMI, Mean ± SD</td>
</tr>
<tr>
<td>Female (%)</td>
</tr>
<tr>
<td>Previous Pregnancy in Females (%)</td>
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<tr>
<td>Ischemic Time, Mean Mins ± SD</td>
</tr>
<tr>
<td>Primary Reason for Tx, Underlying Diagnosis of CAD (%)</td>
</tr>
<tr>
<td>Status 1 at Transplant (%)</td>
</tr>
<tr>
<td>CMV Mismatch (%)</td>
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<tr>
<td>Diabetes Mellitus (%)</td>
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<tr>
<td>Treated Hypertension (%)</td>
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<tr>
<td>Prior Blood Transfusion (%)</td>
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<tr>
<td>Pre-Transplant cPRA, Mean ± SD</td>
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<tr>
<td>Pre-Transplant Creatinine Mean ± SD</td>
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<tr>
<td>Insertion of MCS Device</td>
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Prior Desensitization Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib + Plasmapheresis</td>
<td>70.0% (7/10)</td>
</tr>
<tr>
<td>Bortezomib + Plasmapheresis + IVIG</td>
<td>10.0% (1/10)</td>
</tr>
<tr>
<td>IVIG + Plasmapheresis</td>
<td>10.0% (1/10)</td>
</tr>
<tr>
<td>None</td>
<td>10.0% (1/10)</td>
</tr>
<tr>
<td>Crossmatch Type</td>
<td>Results, N=10</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>T-Flow Cytometry Crossmatch</td>
<td>117 ± 145 MCS</td>
</tr>
<tr>
<td>B-Flow Cytometry Crossmatch</td>
<td>220 ± 96 MCS</td>
</tr>
<tr>
<td>T-Cell Complement-Dependent Cytotoxicity Crossmatch</td>
<td>All negative</td>
</tr>
<tr>
<td>B-Cell Complement-Dependent Cytotoxicity Crossmatch</td>
<td>All negative</td>
</tr>
</tbody>
</table>

Positive T-Flow >50 MCS  Positive B-Flow >100 MCS
## Preliminary Outcomes

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>N=10</th>
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</thead>
<tbody>
<tr>
<td>% of Patients with DSA at 1 Month Post-Transplant</td>
<td>80.0%</td>
</tr>
<tr>
<td>1-Year Freedom from Treated Infection</td>
<td>90.0%</td>
</tr>
<tr>
<td>1-Year Actuarial Survival</td>
<td>90.0%</td>
</tr>
<tr>
<td>1-Year Actuarial Freedom from Cellular Rejection (ISHLT ≥2R)</td>
<td>100.0%</td>
</tr>
<tr>
<td>1-Year Actuarial Freedom from Antibody-Mediated Rejection (AMR ≥2)</td>
<td>77.8%</td>
</tr>
<tr>
<td>1-Year Actuarial Freedom from Any Treated Rejection</td>
<td>80%</td>
</tr>
<tr>
<td>Average 6-Month Left Ventricular Ejection Fraction (%)*</td>
<td>65.0 ± 2.6</td>
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</tbody>
</table>

* No patient with reduced LVEF
ABO Incompatible (ABOi) Transplantation

• Well established in pediatric solid organ transplantation including hearts
• In adults, experience is greatest in living donor kidney transplantation (LDKT)
• In Japan constitutes 14% of kidney transplants and 30% of LDKT
• May lower incidence of AMR due to early antibody depletion
• Potential to significantly expand the donor pool – approx. 35% of donors ABOi.
Outcomes after ABO-incompatible heart transplantation in adults: A registry study
Cumulative death or retransplantation

Cumulative death or retransplantation of ABO-incompatible and ABO-compatible heart transplants for the entire study period (A) and for grafts surviving the first year (B).

Bergenfeldt H et al, JHLT Volume 34, Issue 7, 2015, 892–898
Outcomes after ABO-incompatible heart transplantation in adults: A registry study death or retransplantation by era

Overall incidence of death or retransplantation for ABO-incompatible and ABO-compatible heart transplants during the periods 1988-2005 (A) and 2006-2011 (B).

Bergenfeldt H et al, JHLT Volume 34, Issue 7, 2015, 892–898
Summary

- Number of sensitized patients awaiting heart transplant continues to increase
- Sensitized patients spend a longer time on the wait-list, have increased wait-list mortality
- There are no randomized trials of desensitization in solid organ transplantation
- Efficacy of treatment varies widely – **Not All Sensitized Patients Are Equal**
- Combination therapies appear to be more effective
- Patients transplanted following desensitization appear to have acceptable survival although allograft rejection rates remain high
- There is a suggestion that even if therapies are ineffective at significantly reducing alloantibody burden, there may be sufficient immunomodulation to permit transplantation with acceptable outcomes
- Adult ABOi heart transplantation is an emerging area with promise of acceptable long-term outcomes
- The proposed US Heart Allocation Scheme will not allow priority for sensitized patients, unlike the Canadian scheme or new US Kidney Transplant Allocation Scheme