Outcomes of Pre-Transplant Antibodies: Non-MCS and MCS Patients

Jon Kobashigawa, MD
Cedars-Sinai Heart Institute

I have financial relationships to disclose:
Research Grants, Advisory Boards, Speaker honoraria with Novartis, XDx, TransMedic.

My presentation does not include discussion of off-label or investigational use.

Sensitization

- Sensitization in patients awaiting heart transplantation is due to circulating antibodies from prior blood transfusions, mechanical circulatory support (MCS) devices, and pregnancy.1
- Sensitized patients have an increased risk for rejection, hemodynamic compromise rejection, cardiac allograft vasculopathy and mortality.2-3
- Heart failure patients who require MCS implantation appear to be at higher risk for sensitization.4

Virtual Crossmatch

- Solid phase assays have been used to predict compatibility of donor organs by comparing the potential recipient’s HLA-specific antibodies with the HLA type of the prospective donor, an approach called the virtual crossmatch. ¹, ²
- The virtual crossmatch negates the need to send recipient blood to Organ Procurement Organizations for a prospective crossmatch, thus increasing the donor pool for that patient.

¹ R. Pei et al., Transplantation 75 (2003), pp. 46–46.

Calculated PRA (cPRA)

- The cPRA is the percentage of donor hearts in a given population to which a heart transplant candidate has significant anti-HLA antibodies.
- The corresponding antigens to these antibodies are deemed unacceptable. Those potential donors with these unacceptable antigens are automatically turned away.
- The threshold to determine when an anti-HLA antibody is significant is defined by the heart transplant program and is usually dependent on the strength of the antibody.
- The higher the cPRA, the harder it is to find a suitable donor (e.g., 70% cPRA means that 70% of donors will be automatically turned away).

Registry Outcomes of Patients with Pre-transplant PRAs

- Retrospective study in 8,160 heart transplant recipients
- Used data from UNOS/OPTN registry, 2000–2004
- Demonstrated relationship between higher PRA levels at time of transplant and post transplant
  - Lower patient survival
  - Higher first-year rejection rates

Multivariate Cox Proportion Hazard Regression of Patient Survival

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA (continuous variable)</td>
<td>1.005</td>
<td>1.002 – 1.009</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRA 1% - 10%</td>
<td>1.17</td>
<td>0.96 – 1.42</td>
<td>0.12</td>
</tr>
<tr>
<td>PRA 11% - 25%</td>
<td>0.94</td>
<td>0.99 – 1.00</td>
<td>0.73</td>
</tr>
<tr>
<td>PRA &gt; 25%</td>
<td>1.4</td>
<td>1.09 – 1.77</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Relationship Between cPRA and Post-Transplant Outcomes

- Although the calculated panel reactive antibody (cPRA) value is used to assign allocation priority to kidney transplant candidates in the United States, the relationship between cPRA and outcomes on the heart transplant waiting list is unknown.
- From the United Network for Organ Sharing Registry, a study cohort was composed of 3,855 adult candidates listed for heart transplant between 2006 and 2013 with active waiting time.
  - The cohort was divided into five groups by increasing cPRA.
- Outcomes were assessed using competing risks and subhazard regression analyses.

Kransdorf E. Unpublished data. Cedars-Sinai Heart Institute
**Post-Transplant Mortality According to Pre-Transplant cPRA**

Kransdorf E. Unpublished data. Cedars-Sinai Heart Institute

**cPRA Study Conclusions**

- Sensitized candidates had increased mortality at 3 years post-transplant, and that the increased risk of mortality was not linearly related to the CPRA (after cPRA>20%).
- The use of the virtual crossmatch, in conjunction with the cell-based crossmatch did not fully attenuate the post-transplant risk of sensitization.
- The reasons for this increased post-transplant mortality have not been formally addressed in our study, but could be due to:
  - Anti-DQA/DP antibodies (Bachelet:2016), which are not accounted for in the current cPRA calculation,
  - The increased risk of developing de novo DSA in sensitized candidates (Clerkin:2016)

Kransdorf E. Unpublished data. Cedars-Sinai Heart Institute

**Post Transplant Outcomes of the Treated Sensitized Patient**

- 21 treated patients with pre-transplant PRA 50% - 100%
  - PRAs decreased by a mean reduction of 40% and all patients underwent successful heart transplantation with negative prospective or virtual crossmatch
  - Immediately post transplant depending on rejection risk:
    - 6/21 patients were administered Thymoglobulin followed by IVIG
    - 11/21 patients received plasmapheresis immediately postop
    - Maintenance immunosuppression included tacrolimus, mycophenolate mofetil and routine corticosteroids.

Kobashigawa J. Clinical Transplant 2010; 25(1):E61-67
Heart Transplant Outcomes of the Pre-Transplant Desensitized Patient

<table>
<thead>
<tr>
<th></th>
<th>Freedom from 1st Year Rejection</th>
<th>Freedom from 5-Year CAV†</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated Group (N=21)</td>
<td>57.1%*</td>
<td>66.7%</td>
<td>81.0%</td>
</tr>
<tr>
<td>Control (N=493)</td>
<td>88.8%</td>
<td>74.6%</td>
<td>77.3%</td>
</tr>
</tbody>
</table>

† CAV, Cardiac allograft vasculopathy, defined as >30% stenosis in any vessel on angiography.
*Compared to controls, p<0.05
(Data reflect actuarial results)

Kobashigawa J. Clinical Transplant 2010; 25(1):E61-67

Clinical Challenges in Sensitized MCS Patients

- Are pre-transplant circulating antibodies in a MCS patient bad?
- If circulating antibody levels in the pre-transplant MCS patient are found to be significant, should one intervene?
- What can be done to lower these antibody levels?
- Does lowering of antibody levels make a difference in clinical outcome?
- What approach do you take for pretransplant desensitized patients after heart transplantation?

Circulating Antibodies and Mechanical Circulatory Support Devices

- LVADs have been demonstrated to be responsible for sensitization through up-regulation of the immune system and increased antibody production.1
- This is due to their specific physical properties, their blood contacting surface, and the frequent need for blood product support.
- Studies3-5 on outcomes of patients with LVADS who undergo heart transplantation suggest that:
  - LVAD patients have survival outcomes similar to those of nonbridged patients after heart transplantation despite significantly higher immunologic risk due to sensitization.
  - It is possible that immunomodulatory therapy helped to counter this higher immunologic risk.

1 Delave et al. J Heart Lung Transplant 2010; 29: 636-43
4 Smedira et al. J Thorac Cardiovasc Surg 2010; 139: 1295-305
5 Alba et al. Euro J Heart Fail 2011; 13: 785-95
Are Sensitized MCS patients at risk for post-transplant rejection?

Cedars-Sinai Heart Transplant Program

- Between 1994 and 2012, we evaluated 136 sensitized (PRA≥10%) heart transplant patients and divided them into the following groups:
  - Non-MCS PRA ≥ 10% (N = 71)
  - MCS PRA ≥ 10% (N = 65)
- Routine Immunosuppression:
  - Most patients with PRA ≥ 10% received thymoglobulin induction
  - Since 1998 all patients on TAC/MMF maintenance immunosuppression

Kobashigawa, unpublished data, Cedars-Sinai Heart Institute
Methods

- Post transplant outcomes included:
  - 1-Year Freedom from Treated Cellular Rejection
  - 1-Year Freedom from Treated Antibody Mediated Rejection
  - 3-Year Actuarial Survival
  - 3-Year Freedom from Cardiac Allograft Vasculopathy (CAV; defined as an angiographic stenosis ≥ 30%)
  - 3-Year Freedom from non-fatal major adverse cardiac events (NF-MACE, defined as MI, CHF, need for PCI or pacemaker, stroke)

Kobashigawa, unpublished data, Cedars-Sinai Heart Institute

<table>
<thead>
<tr>
<th>MCS Sensitized VAD Patient Results</th>
<th>Sensitized MCS (n=65)</th>
<th>Sensitized Non-MCS (n=72)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Year Freedom from Cellular Rejection</td>
<td>81.5%</td>
<td>77.5%</td>
<td>0.53</td>
</tr>
<tr>
<td>1-Year Freedom from Antibody-Mediated Rejection</td>
<td>81.5%</td>
<td>62.0%</td>
<td>0.01</td>
</tr>
<tr>
<td>3-Year Actuarial Survival</td>
<td>81.5%</td>
<td>84.5%</td>
<td>0.62</td>
</tr>
<tr>
<td>3-Year Freedom from CAV</td>
<td>92.3%</td>
<td>97.2%</td>
<td>0.20</td>
</tr>
<tr>
<td>3-year Freedom from NF-MACE</td>
<td>93.8%</td>
<td>96.4%</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Kobashigawa, unpublished data, Cedars-Sinai Heart Institute

MCS Sensitized VAD Patient Conclusions

- Compared to sensitized non-VAD patients, sensitized VAD patients appear to have less antibody mediated rejection after heart transplantation, suggesting that their immune response may be truncated after removal of the VAD after undergoing heart transplant.
- Further study into the mechanisms of this observed response is being pursued.
Contemporary MCS Sensitized Patients (2010-2014) and Post-Transplant Antibody Results

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Sensitized VAD (N=19)</th>
<th>Sensitized Non-VAD (N=55)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Year Survival</td>
<td>94.7%</td>
<td>94.5%</td>
<td>0.997</td>
</tr>
<tr>
<td>1-Year Freedom from</td>
<td>94.4%</td>
<td>89.9%</td>
<td>0.613</td>
</tr>
<tr>
<td>Antibody-Mediated Rejection</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sensitized VAD (n=19) Baseline 12-Months P-Value

- Class I Mean PRA %: 56.6 ±39.4 vs. 23.1 ±31.9, P = 0.007
- Class II Mean PRA %: 37.9 ±37.7 vs. 18.2 ±23.1, P = 0.069

Sensitized non-VAD (n=55) Baseline 12-Months P-Value

- Class I Mean PRA %: 37.1 ±33.8 vs. 34.3 ±34.6, P = 0.660
- Class II Mean PRA %: 37.9 ±32.9 vs. 30.8 ±35.9, P = 0.283

Kobashigawa, unpublished data, Cedars-Sinai Heart Institute

When and Why to Use Desensitization Therapy

When:
- Some use a threshold to desensitize when the cPRA >50%.

Why:
- To improve the chances of receiving a compatible donor (which may shorten waiting time).
- To possibly affect outcome after heart transplantation.

Clinical Trials in Organ Transplantation (CTOT-13)

- NIH sponsored clinical trial in status 1 sensitized patients (cPRA > 30%) awaiting heart transplantation
- Patients randomized to bortezomib/plasmapheresis or no therapy
- Primary endpoint included complications while waiting: Death, removal from the waiting list except for improvement of cardiac function, initiation of a MCS, severe infection requiring intravenous antibiotics, cerebral vascular accident, acute renal failure requiring dialysis.
- The study was terminated after 3 patients entered into the study due to lack of enrollment

Heeger, Principal Investigator
Kobashigawa, Protocol Chair
Summary

• Sensitized patients awaiting heart transplant appear at risk for poor outcome post-transplant.
• Sensitized MCS patients may not have increased risk for post-transplant poor outcome due to a truncated immune response post-transplant (once the MCS is removed).
• Treatment of the sensitized patient depends on the calculated PRA and risk tolerance of the individual heart transplant program.
• Specialized post heart transplant care for sensitized patients may be needed to optimize outcomes.

Thank You