THE NEW KIDNEY ALLOCATION SYSTEM: A POTENTIAL EXPANSION OF THERAPEUTIC APHERESIS UTILIZATION

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Disclosure

• I have nothing to disclose that is relevant to this presentation
Outline

• History of ABO-i Renal Transplantation
  • Early experience
• “Minor” vs. “Major” incompatibility
• National Minor ABOi Allocation
  • Old vs. new system
• Unresolved Issues
History of ABO-i Renal Txp.

Hume, et al, J Clin Invest

• One case of ABO-I (Donor B → Recipient O)
• “...we do not feel that renal transplantation in the presence of blood incompatibility is wise, if only on the basis of possible local damage to the kidney.”

• Very few ABO-I transplants done until 1970s
History of ABO-i Renal Txp.

- 1970s: “Minor” ABO-i renal txp (A2 → O and B) became more common
  - Low initial titers necessary (1:4)
  - Poor outcomes led to abandonment of practice in 1980s

| A<sub>1</sub> and A<sub>2</sub> Subgroups* |
|-------------------------------|------------------------------|-----------------|-----------------|-----------------|
| Anti-A antisera | Anti-A<sub>1</sub> antisera | Anti-H lectin | ABO antibodies in serum | # of antigen sites per RBC |
| A<sub>1</sub> | 4+ | 4+ | 0 | Anti-B | 900 x 10<sup>3</sup> |
| A<sub>2</sub> | 4+ | 0 | 3+ | Anti-B & anti-A<sub>1</sub> | 250 x 10<sup>3</sup> |

History of ABO-i Renal Txp.

- 1980: Accidental A → O transplant, used plasmapheresis to reverse rejection/damage
  - Immediate reversal of intrarenal vascular coagulation
  - Despite an anti-A antibody rebound weeks after transplantation, graft biopsies were negative for intravascular coagulation (Accommodation)
Accommodation

- Absence of allograft injury in the presence of donor-specific antibodies
- Evidence:
  - Protocol biopsies 6-12 months post transplant are C4d-positive
- Proposed mechanisms
Accommodation Contd

- Accommodation may be the body’s natural balancing act (immune-related injury vs. ‘infection’)
- In ABOi renal transplantation, keeping the titers low is critical the first few weeks post-tx
- Long term, down-regulation of A/B antigens may contribute
A2/A2B-to-B Allocation System

- Midwest Transplant Network
- Designed to increase access for ABO-B recipients on deceased donor wait list
## Table 1: Blood group/subgroup phenotype frequencies by ethnicity

<table>
<thead>
<tr>
<th>Blood group</th>
<th>Blood group phenotype frequencies</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
</tr>
<tr>
<td>B</td>
<td>9%</td>
</tr>
<tr>
<td>A</td>
<td>44%</td>
</tr>
<tr>
<td>A(_1)</td>
<td>34%</td>
</tr>
<tr>
<td>A(_2)</td>
<td>10%</td>
</tr>
<tr>
<td>O</td>
<td>44%</td>
</tr>
<tr>
<td>AB</td>
<td>3%</td>
</tr>
</tbody>
</table>

A2/A2B-to-B Allocation System

- Midwest Transplant Network

- 2001-2013: ABO-B candidates received 10% more kidney transplants than previous period
- Transplant rates for ABO-B candidates
  - 11.9% (1989-2001)
  - 13% (2001-2013)
- Composition of waitlist: 16% ABO-B Candidates
MTN Early Principles

• Pre-Transplant Anti-A Titers Matter
  • 14/14 pts w/ anti-A titers < 8 had 100% early and long term graft function
  • 6/11 pts w/ anti-A titers ≥ 8 lost function at 1 month, and most never regained

• Standard Immunosuppression Is Sufficient
  • No apheresis, splenectomy, IVIg
  • As long as anti-A titers are < 8
MTN Early Principles

- Anti-A titers are “relatively” stable, and usually low
  - Test every three months
  - No need for immediate pre-transplant testing
  - 80%-90% of ABO-B candidates have consistently low anti-A titers
Average Monthly Anti-A Titers
(N = 2235 Tests)
MTN Early Principles

- ABO-B candidates rarely have total titers (IgG and IgM) higher than IgG-only titers
- DTT-treated serum, using a tube titration method, became the norm (UNOS Method)

- IgM antibodies may be clinically-relevant
December 2014: New KAS

- Old: Anti-A titers performed with UNOS titration method
- New: Centers may use whatever titration method they choose

- Old: Titers were mandated to be performed every 3 months
- New: Regular titer measurements are optional

- Old: Candidates with titers >4 were automatically ineligible
- New: Centers may transplant regardless of titer values
Unresolved Issues

- Differential Antigen Expression

Böhmig, G. A. et al. Nat. Rev. Nephrol. advance online publication 1 September 2015
Unresolved Issues

- Differential Antigen Expression

A2-transferase

Kidney

Böhmig, G. A. et al. Nat. Rev. Nephrol. advance online publication 1 September 2015
Unresolved Issues

• Which Titer method? (Masterson, et al,
American Journal of Transplantation 2014; 14: 2807–2813)

Table 3: Blood group incompatibilities and antibody titers by three methods

<table>
<thead>
<tr>
<th>Donor blood group</th>
<th>Recipient blood group</th>
<th>Tube titer</th>
<th>Ortho titer</th>
<th>Diamed gel card titer</th>
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</thead>
<tbody>
<tr>
<td>A1</td>
<td>O</td>
<td>32</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>A1</td>
<td>O</td>
<td>64</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>A1^c</td>
<td>B</td>
<td>16</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>A2</td>
<td>O</td>
<td>32</td>
<td>4</td>
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<td>O</td>
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<td>A1B</td>
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<tr>
<td>A1B</td>
<td>A</td>
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<td>1</td>
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<tr>
<td>A1B^d</td>
<td>B</td>
<td>32</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>
Unresolved Issues

• Why aren’t post-transplant anti-A titers monitored??
  • At least for the first few weeks
  • Very few studies
Unresolved Issues

- Different Apheresis Methods
Summary

• Minor ABOi renal transplant have outcomes similar to ABOc transplants
  • Provided initial titers are low
• Centers now have the option to employ TA for candidates that have titers > 4
  • Useful for highly HLA-sensitized recipients
• Post-transplant titer monitoring may be useful
  • Employ TA if titers increase
Thank You!

Questions?