THE ROLE OF APHERESIS IN INCOMPATIBLE KIDNEY TRANSPLANTATION

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November 20th 2015
No conflicts of interest to disclose
The need for incompatible transplants
Desensitization protocols
  • Hopkins experience
  • Columbia experience
  • Korean experience
ASFA recommendations
Based on OPTN data as October 23rd, 2015
OPTIONS TO INCREASE DONOR POOL

- Deceased donor
- Living donor
- Pair kidney donation (PKD)
- Desensitization (HLA, ABO incompatible)
- Combined PKD and desensitization
- Other:
  - Non-A1 organs (A2, reduced expression of A into B recipients)

Based on OPTN data as October 23rd, 2015
UNOS Allocation system
Anti-A titers < 8
No need for desensitization
No need for post-transplant antibody follow up
Antibodies binding to cognate antigen on the allograft can result in rejection.

Antibodies
- HLA
- ABO
- Other: Endothelial, Angiotensin, Unknown

Rejection
- Hyperacute
- Acute antibody mediated rejection
- Acute cellular rejection
- Chronic rejection
WHY DO WE DARE TO PERFORM INCOMPATIBLE TRANSPLANTS?

High mortality in waiting list
Ability to remove pre formed antibodies (desensitization protocols)
Immunosuppressive strategies
Ability to remove newly formed antibodies [antibody mediated rejection (AMR) protocols]
Critical components

- Antibody removal
- Pre-transplant immunosuppression
- B cell depletion
ABO antibody titers
  • Tube, gel methods
  • Room temperature (RT), antihuman globulin phase (AHG)

Therapeutic plasma exchange
  • Pre and post transplant
  • Followed by IVIG
  • Goal: Pre-transplant titer < 16
  • Continue monitoring of ABO antibody titers
    • Significance in prediction of antibody mediated rejection is uncertain
DESENSITIZATION FOR ABO INCOMPATIBLE TRANSPLANTS

Tobian, Transfusion 2009
Titers

TABLE 1. The number of planned pre- and posttransplant PP/IVIG treatments correlate with the starting isohemagglutinin titer

<table>
<thead>
<tr>
<th>Starting isoagglutinin AHG titer</th>
<th>Pretransplant PP/IVIG treatments</th>
<th>Posttransplant PP/IVIG treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;16</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>16–32</td>
<td>3</td>
<td>2–3</td>
</tr>
<tr>
<td>64</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>128</td>
<td>5–6</td>
<td>4</td>
</tr>
<tr>
<td>256</td>
<td>7–8</td>
<td>4</td>
</tr>
<tr>
<td>512</td>
<td>9–10</td>
<td>5</td>
</tr>
<tr>
<td>&gt;512</td>
<td>&gt;10</td>
<td>6</td>
</tr>
</tbody>
</table>

PP, plasmapheresis; AHG, anti-human globulin.

Outcomes

TABLE 4. Patient and graft survival among 60 ABOi kidney transplant recipients transplanted at the Johns Hopkins Hospital between 1999 and 2007

<table>
<thead>
<tr>
<th>ABOi cohort</th>
<th>Years posttransplant</th>
<th>Graft survival(^a) (%)</th>
<th>Patient survival(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 yr</td>
<td>98.3</td>
<td>96.3</td>
</tr>
<tr>
<td></td>
<td>3 yr</td>
<td>92.9</td>
<td>96.3</td>
</tr>
<tr>
<td></td>
<td>5 yr</td>
<td>88.7</td>
<td>89.4</td>
</tr>
</tbody>
</table>

\(^a\) Death-censored graft survival; 4 graft losses occurred in the first era cohort and were secondary to non-compliance (n=1), recurrent disease (n=2), and thrombotic microangiopathy (n=1).

\(^b\) All 3 patients died with a functioning graft; 3 patient deaths were secondary to West Nile virus, sudden cardiac death, and metastatic liver cancer. ABOi, ABO incompatible.

60 patients
Average plasma exchange: 6 pre and 5 post
AMR: 5.7%
211 patients, TPE 4 pre, 5 post
Goal: decrease DSA until negative CDC cross match
Patient survival, no information on graft survival
16 ABOi, 7 ABOi-XM, 23 XM (2004 – 2006)

Desensitization protocol similar to Hopkins

Anti-A, Anti-B titers tube method

- IgM, saline method
- IgG, antihuman globulin

Anti-HLA

- CDC and flow cytometry
- Luminex, single antigen beads

Outcome: early and late AMR rejection

- biopsies 1, 2 weeks and 1 month, then 3, 6, 12 and 24 months
Median             3                      7                   4
Median          2                       5

Titers: Anti-A/B IgM 32 (16, 64), IgG 32 (16,64)

Padmanabhan, Transplantation 2009
~50% of all patients had AMR, most often in the first 2 weeks
~30% of HLAi patients had ACE, most often in the first 2 weeks
LATE AMR AND ACR (>30 DAYS POST-TX)

(A) Late AMR

(B) Late ACR

Probability of Rejection-free survival

Time Post-Tx (days)

p=0.04

p=0.03

UW Medicine
Padmanabhan Transplantation 2009
<table>
<thead>
<tr>
<th></th>
<th>Graft Survival</th>
<th>Patient Survival</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incompatible</td>
<td>80%</td>
<td>91%</td>
<td>11%</td>
</tr>
<tr>
<td>Conventional</td>
<td>96%</td>
<td>98%</td>
<td>1%</td>
</tr>
</tbody>
</table>
## Long Term Survival of ABOI Kidney Transplants, 2009-2012, Korea

<table>
<thead>
<tr>
<th></th>
<th>ABO- Compatible (n = 396)</th>
<th>ABO- Incompatible (n = 73)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient survival</strong></td>
<td></td>
<td></td>
<td>.136</td>
</tr>
<tr>
<td>1 year</td>
<td>99.0%</td>
<td>97.3%</td>
<td></td>
</tr>
<tr>
<td>3 years</td>
<td>98.5%</td>
<td>95.9%</td>
<td></td>
</tr>
<tr>
<td><strong>Graft survival</strong></td>
<td></td>
<td></td>
<td>.386</td>
</tr>
<tr>
<td>1 year</td>
<td>99.7%</td>
<td>98.6%</td>
<td></td>
</tr>
<tr>
<td>3 years</td>
<td>98.7%</td>
<td>98.6%</td>
<td></td>
</tr>
<tr>
<td><strong>Acute rejection episodes (%)</strong></td>
<td>71 (17.9)</td>
<td>10 (13.7)</td>
<td>.380</td>
</tr>
<tr>
<td>AAMR</td>
<td>14 (3.5)</td>
<td>2 (2.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>ACMR</td>
<td>68 (17.2)</td>
<td>10 (13.7)</td>
<td>.464</td>
</tr>
<tr>
<td><strong>Infectious complications (%)</strong></td>
<td>122 (30.8)</td>
<td>16 (21.9)</td>
<td>.126</td>
</tr>
</tbody>
</table>

Desensitization protocol: TPE, Rituximab, Basiliximab, tacrolimus, mycophenolate, steroids.
## Renal transplantation, ABOi

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Category</th>
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</thead>
<tbody>
<tr>
<td>Desensitization, Living donor</td>
<td>1B</td>
</tr>
<tr>
<td>Humoral rejection</td>
<td>1B</td>
</tr>
<tr>
<td>A2/A2B into B, deceased</td>
<td>1B</td>
</tr>
</tbody>
</table>

## Renal transplantation, HLAi

<table>
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<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral rejection</td>
<td>1B</td>
</tr>
<tr>
<td>Desensitization, LD</td>
<td>1B</td>
</tr>
<tr>
<td>Desensitization, DD</td>
<td>2C</td>
</tr>
</tbody>
</table>
Application of flow cytometry to measure anti-A,-B
Role of IgG subclasses in antibody mediated rejection
Immunosuppressive strategies combining anti-CD20 (Rituximab), anti-CD25 (Daclixumab, Baciliximab), anti-plasma cells (Bortezomib) and anti-complement (Eculizumab). Dose, combination, and timing.
Several desensitization strategies

- Antibody removal, immunosuppression, B cell depletion

Incompatible transplants

- Increase donor pool
- Decrease waiting list

TPE proven effective in

- Desensitization protocols
- Antibody mediated rejection
THANKS. QUESTIONS?