Pulmonary AMR – Therapeutic Options & Strategies: The Old and the New

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Disclosures

• Ramsey Hachem
• I have no financial relations with any relevant commercial interests
• I will discuss the “off-label” use of multiple treatments for pulmonary AMR
Introduction

• AMR is an increasingly recognized form of lung rejection

• Most common histology is non-specific lung injury – pneumonitis, DAD

• Diagnosis requires a high index of suspicion & multidisciplinary approach

• Outcomes after AMR remain disappointing
Definition of “Definite AMR is stringent.
4 combinations of “Probable AMR”–
Not all equal in terms of diagnostic certainty between groups of Probable/Possible
## Definite AMR & C4d-negative
Probable AMR

<table>
<thead>
<tr>
<th>Variable</th>
<th>C4d-positive (n = 28)</th>
<th>C4d-negative (n = 45)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of onset of AMR, days</td>
<td>193</td>
<td>161</td>
<td>0.928</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>23 (82%)</td>
<td>32 (73%)</td>
<td>0.359</td>
</tr>
<tr>
<td>Radiographic infiltrates</td>
<td>23 (82%)</td>
<td>36 (80%)</td>
<td>0.821</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>12 (43%)</td>
<td>16 (36%)</td>
<td>0.533</td>
</tr>
<tr>
<td>DSA class</td>
<td></td>
<td></td>
<td>0.504</td>
</tr>
<tr>
<td>Class I only</td>
<td>4 (14%)</td>
<td>3 (7%)</td>
<td></td>
</tr>
<tr>
<td>Class II only</td>
<td>20 (71%)</td>
<td>33 (73%)</td>
<td></td>
</tr>
<tr>
<td>Class I &amp; II</td>
<td>4 (14%)</td>
<td>9 (20%)</td>
<td></td>
</tr>
<tr>
<td>DSA to HLA-DQ</td>
<td>20 (71%)</td>
<td>36 (80%)</td>
<td>0.399</td>
</tr>
<tr>
<td>DSA MFI (mean ± SD)</td>
<td>8764 ± 4141</td>
<td>6839 ± 3993</td>
<td>0.130</td>
</tr>
<tr>
<td>C1q-positive DSA</td>
<td>12/12 (100%)</td>
<td>12/18 (67%)</td>
<td>0.025</td>
</tr>
</tbody>
</table>
CLAD-Free Survival

Log rank p = 0.771

Similar groups with similar treatments
Both groups show poor outcomes

Is C4d deposition a necessary criteria for the diagnosis?
Role of C4d in the Diagnosis

• C4d staining & interpretation problematic
  – ? Possible that these cases are false negatives

• Distinct pathways that cause AMR
  – Complement-independent pathways?

• Distinction may have therapeutic implications
  – If complement inhibitors are considered

• Further studies are necessary
  – Genomic analyses
## Systemic Review
### Treatment in Acute AMR in Kidney Transplantation

<table>
<thead>
<tr>
<th>Reference</th>
<th>AMR definition</th>
<th>Design &amp; intervention</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Böhmig et al, 2007</td>
<td>Banff 1997</td>
<td>RCT; 9-14 IA</td>
<td>Significant benefit, rescue not effective</td>
</tr>
<tr>
<td>Bonomini et al, 1985</td>
<td>Vascular, steroid-resistant</td>
<td>RCT; 3-7 PLEX</td>
<td>Benefit, 7 vs. 17 at 2 wks</td>
</tr>
<tr>
<td>Blake et al, 1990</td>
<td>Vascular</td>
<td>RCT; 5 PLEX</td>
<td>No benefit</td>
</tr>
<tr>
<td>Kirubakaran et al, 1981</td>
<td>Vascular</td>
<td>RCT; 8 PLEX</td>
<td>Trend to harm</td>
</tr>
<tr>
<td>Allen et al, 1983</td>
<td>Vascular, steroid-resistant</td>
<td>RCT; 6 PLEX</td>
<td>No benefit</td>
</tr>
</tbody>
</table>

*None of these studies included IVIG/PLEX*  

Transplantation 2012; 94: 775  
Am J Transplant 2014; 14: 255
Rituximab for Renal AMR

- 21 centers in France, RCT
  - Enrollment between 2008 – 2011
  - Rituximab vs. Placebo
    - In addition to PLEX, IVIG, CS
- 1 endpoint: graft loss or no improvement on d 12
- Additional doses of Rituximab on d 12 for insufficient efficacy

Transplantation 2016; 100: 391
Rituximab for Renal AMR

- 40 patients enrolled, 38 treated
- Placebo: n = 19, Rituximab: n = 19
- Placebo patients receiving rescue Rituximab, n = 8
- Rituximab patients receiving rescue Rituximab, n = 6
- No difference in primary endpoint
- No difference in graft loss at 1 year

Transplantation 2016; 100: 391
Principles of Treatment: Multiple interventions

- Deplete circulating DSA: does not suppress further production, may stimulate rebound
  - PLEX, immunoadsorption

- Suppress B-cells, plasma cells:
  - IVIG, Rituximab, Bortezomib, Carfilzomib
  - MMF, ATG: may be of benefit by downregulating B cell response by decreasing T-cell

- Mitigate antibody-mediated lung injury
  - Steroids, IVIG, Eculizumab
Literature on Treatment

• Imported treatment options: without appropriate clinical trials in AMR

• Dearth of data: No RCT or head-to-head comparison
• Multiple concurrent interventions

• Individualized regimens based on clinical course & response to “1st line” intervention

• Difficult to make conclusions about relative efficacy of any single intervention or regimen

• Standardizing definition of AMR is first step to allow multicenter trials or comparisons of regimens.
Treatment & Outcomes: Definite and probable AMR

- Lobo et al (CS, PLEX, RTX, IVIG, BOR):
  - 7/10 died (5 due to AMR, 2 due to sepsis after treatment)

- Otani et al (CS, PLEX, RTX, IVIG):
  - 5/9 initial clinical improvement and decreased MFI
    - 2/5 subsequent RAS & death (363, 610 d)
  - 4/9 progressive CLAD & death: no decrease in MFI
    - 2 progressive RAS & death (79, 180 d)
    - 2 progressive BOS & death (179, 288 d)

J Heart Lung Transplant 2013; 32: 70
Transpl Immunol 2014; 31: 75
Wash U treatment approach: individualized regimen, based on severity of illness, clinical course and response to therapy. All patients met criteria for definite AMR.

<table>
<thead>
<tr>
<th>Patient</th>
<th>ATG</th>
<th>IVIg dose (number of doses)</th>
<th>Rituximab</th>
<th>Plasma exchange (number of treatments)</th>
<th>Bortezomib dose (number of doses)</th>
<th>Eculizumab</th>
<th>Survived to discharge</th>
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<tbody>
<tr>
<td>1</td>
<td>Yes*</td>
<td>None</td>
<td>—</td>
<td>Not done</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
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<tr>
<td>2</td>
<td>—</td>
<td>1 g/kg (1)</td>
<td>375 mg/m²</td>
<td>12</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
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<tr>
<td>3</td>
<td>—</td>
<td>1 g/kg (1)</td>
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<td>—</td>
<td>—</td>
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<tr>
<td>4</td>
<td>—</td>
<td>1 g/kg (1)</td>
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<td>—</td>
<td>—</td>
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<tr>
<td>5</td>
<td>—</td>
<td>0.5 g/kg (2)</td>
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<td>—</td>
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<td>6</td>
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<td>—</td>
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<td>7</td>
<td>—</td>
<td>0.5 g/kg (1)</td>
<td>375 mg/m²</td>
<td>5</td>
<td>—</td>
<td>—</td>
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<td>8</td>
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<td>—</td>
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<tr>
<td>9</td>
<td>—</td>
<td>1 g/kg (1)</td>
<td>375 mg/m²</td>
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<td>—</td>
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<td>10</td>
<td>—</td>
<td>0.5 g/kg (2)</td>
<td>375 mg/m²</td>
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<tr>
<td>11</td>
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<td>0.5 g/kg (1)</td>
<td>—</td>
<td>3</td>
<td>—</td>
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<tr>
<td>12</td>
<td>—</td>
<td>0.5 g/kg (1)</td>
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<td>14</td>
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<td>1 g/kg (1)</td>
<td>375 mg/m²</td>
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<td>15</td>
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<tr>
<td>16</td>
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<td>0.5 g/kg (3)</td>
<td>375 mg/m²</td>
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<td>17</td>
<td>—</td>
<td>0.5 g/kg (1)</td>
<td>375 mg/m²</td>
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<td>—</td>
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<td>18</td>
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<td>1 g/kg (2)</td>
<td>375 mg/m²</td>
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<td>1.3 mg/m² (8)</td>
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<tr>
<td>19</td>
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<td>375 mg/m²</td>
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<td>1.3 mg/m² (1)</td>
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<tr>
<td>20</td>
<td>—</td>
<td>0.5 g/kg (1) 1 g/kg (2)</td>
<td>375 mg/m²</td>
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<td>—</td>
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<tr>
<td>21</td>
<td>—</td>
<td>1 g/kg (3)</td>
<td>375 mg/m²</td>
<td>5</td>
<td>1.3 mg/m² (4)</td>
<td>Yes³</td>
<td>No</td>
</tr>
</tbody>
</table>

J Heart Lung Transplant 2013; 32: 1034
CLAD after AMR with individualized therapy

- 9/21 cleared DSA
  - All 9 who cleared DSA improved
- 15/21 initial improvement
- 6/21 died AMR
- 13/14 developed CLAD (median 114 d after AMR)

J Heart Lung Transplant 2013; 32: 1034
Survival after AMR

15/21 died
AMR, n = 6
CLAD, n = 9

J Heart Lung Transplant 2013; 32: 1034
Treatment & Outcomes: Definite and Probable AMR

- 22 patient with definite & probable AMR
- PLEX + RTX + IVIG, n = 17
- PLEX alone, n = 3
- IVIG alone, n = 2
- DSA clearance associated with better survival
- DSA cleared in 8/10 who survived and 2/12 who died

Roux , Am J Transplant 2016; 16: 1216
Carfilzomib: Definite, probable and possible AMR

- 2nd generation proteasome inhibitor
- Binds irreversibly resulting in permanent inhibition & plasma cell apoptosis
- 14 patients with definite, probable, & possible AMR
- Carfilzomib + PLEX + IVIG
- Carfilzomib response: loss of C1q binding, n = 10

Am J Transplant 2017; In Press
Carfilzomib-based Therapy

BOS

responders
p=0.05
nonresponders

RAS

responders
p=0.19
nonresponders

Days post CFZ
Freedom From BOS

Days Post CFZ
Freedom From Death

p=0.47

Am J Transplant 2017; In Press
Eculizumab

- Monoclonal antibody to C5 inhibiting cleavage into C5a & C5b
- Case report of patient who could not be desensitized and developed hyperacute rejection
- Eculizumab with IVIG, Bortezomib, PLEX Rituximab
- Hyperacute rejection resolved
- Sustained clinical response 1 year after transplant
- Persistent DSA

J Heart Lung Transplant 2012; 31: 1325
Eculizumab “Resistance”

• Cases of renal AMR in spite of Eculizumab treatment
• Cases of renal AMR that don’t respond to Eculizumab
  – C4d-negative AMR
  – C1q-negative DSA
• Highlight complement-independent pathways of AMR
Better Diagnostics

• Standardizing AMR definition is critical to ensure studies can be done.

• Current diagnostic criteria are crude: Nonspecific histologic changes, C4d issues, clinical mimics of graft dysfunction.

• Need for better precision to improve treatment decisions

• Transcriptome analysis/gene microarray
  – Effective in identifying AMR in kidney & highlighted C4d negative AMR
  – Endothelial genes, NK cells, IFN-γ

• INTERLUNG study: development of molecular microscope diagnostic report in lung

Am J Transplant 2009; 9: 2312
Am J Transplant 2013; 13: 971
Curr Opin Organ Transplant 2015; 20: 359
Exceptional Outcomes

3/3/2008

FVC = 5.5 L (102%)
FEV\(_1\) = 4.32 L (101%)

2/22/2017

Respiratory failure
Definite AMR
Treated with CS, PLEX, IVIG, RTX

J Heart Lung Transplant 2009; 28: 96
Ms. 1

Post transplant course

- PFTs: Progressive improvement and stabilization
- Clinically stable, active
- Complications:
  - History of pneumonia post-operatively. Resolved.
  - History of Grade 2 ACR at 6 months out. Negative C4d. Resolved. Recent biopsy negative.
  - New screening DSA at 3 years: DQ5 mild, DQ 6 strong C1q negative

Ms. 2

Post transplant course

- Did well clinically over the first year. Progressively more dyspneic.
- Complications:
  - Drop in FEV1 by 18% at 20 months with continued progressive decline.
  - Biopsy negative for ACR or infection. + ALI, fibrin exudates, capillaritis. Negative C4d
  - New DSA at 18 months: DQ7 strong, DQ 5 moderate A-2 moderate C1q negative
Question

Would you treat either of these patients for Pulmonary AMR?

1. Ms. 1
2. Ms. 2
3. Both
4. Neither
Questions regarding treatment

• **Who do we treat?**
  - Definite, probable, possible?
  - Based on risk factors of the recipient?
  - Consider adverse effects?

• **When do we treat?**
  - Asymptomatic or wait for symptoms?
  - “Prophylaxis”? 
  - Only with graft dysfunction?

• **How do we treat?**
  - Do we treat all antibodies the same?
  - How many courses/cycles of treatment is appropriate?
  - What therapies are best?

• **What are our goals of therapy?**
  - decreased ab titers, improved graft fxn, freedom from CLAD
Conclusions

• Insufficient evidence to guide treatment
• Optimal treatment is unknown
• AMR reversible cause of graft failure
• High incidence of subsequent CLAD
• Poor allograft survival
• Standardized definition facilitates research
• RCTs comparing existing treatments & doses