Treatment of Chronic Antibody Mediated Rejection

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Disclosures:

Served on Advisory Boards for Genentech Scientific/ROCHE, True North/iPierian, Alexion, Novartis, and Hansa Medical

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I have been involved in clinical trial design for some of the off label drugs I will be discussing.

Objectives

• To understand the phenotypes and natural history of untreated chronic AMR and its effect on graft survival.

• To gain an appreciation for treatment modalities that have a mechanism of action that might prove effective for reversing chronic AMR or prolonging allograft half-life.
De Novo HLA DSA is Common and Leads to Graft Failure


Development of De Novo HLA DSA is Associated With Allograft Loss


AMR Is Associated With A Poor Outcome

Effectiveness of therapy may depend upon:

- Target
- Strength
- Timing
- Ability of DSA to Bind Complement
- Ability of DSA to Produce Microcirculation Inflammation
- Presence of Renal Dysfunction

Chronic AMR may result from De Novo DSA formation, incomplete elimination of DSA following Acute AMR, or persistence of preformed DSA after Desensitization.

### DSA Fate By Specificity After Plasmapheresis

<table>
<thead>
<tr>
<th>Specific</th>
<th>Eliminated</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>cI</td>
<td>74%</td>
<td>26%</td>
</tr>
<tr>
<td>cII (DR, DQ)</td>
<td>56%</td>
<td>44%</td>
</tr>
<tr>
<td>DR51, 52, 53</td>
<td>20%</td>
<td>80%</td>
</tr>
<tr>
<td>Isoagglutinins</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>


### Allograft Survival Is Lower With Class II DSA

1. Bentall et al. AJT 2013; 13:76
The Significance of AMR Varies By The Antibody’s Ability To Bind Complement: Outcomes of C4d+ vs. C4d- AMR

However, Antibodies That Do Not Bind Complement Can Have Clinical Significance

Post Treatment DSA and C1q: Is There Both A Quantitative and Qualitative Difference in DSA

\[\text{DSA+/C1q+ = Higher risk of graft loss}\]
SOC PP/IVIg Treatment Protocol is Effective Therapy for Acute AMR but has Limited Success with Chronic AMR

Anti-CD20
Steroid bolus or α-thymocyte globulin
PP: single plasma volume exchange
IVIG: 100 mg/kg following each PP treatment (CMV hyperimmune globulin)

Rituximab as Add-On Therapy to SOC did not Show Improved Outcomes for Acute AMR Compared to SOC Alone in a Multi-Center Double-Blind Randomized trial

Repeat cycle every 21 days
Poor Response to Bortezomib as Add-On to SOC for Chronic AMR

1Alachkar et al. Transplantation; 97:1240.

Bortezomib Differentially Effects Class I vs. Class II HLA Antibody

1Philogene et al., Transplantation. 2014; 98:660.

Tocilizumab (anti-IL-6R mAb) Treatment for Chronic AMR and TG: Failed SOC Patients

75 Patients with Chronic Active ABMR +/- Transplant Glomerulopathy (TG)

39 Patients Treated with IVIG + Rituximab +/- PLEX (SOC)

37 Patients who failed IVIG + Rituximab + PLEX Rx with Tocilizumab 8mg/kg monthly 6-18M

Tocilizumab vs. SOC in Patients with Established Tg

Classical Complement Pathway in Acute AMR in Sensitized KTRs

Positive Crossmatch Kidney Transplant Recipients Treated With Eculizumab: Outcomes Beyond 1 Year

Decreased ABMR 6.7% vs. 43.8% but no effect on Tg at 2 years

<table>
<thead>
<tr>
<th>Transplant Glomerulopathy in Controls versus Eculizumab</th>
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</thead>
<tbody>
<tr>
<td>Eculizumab*</td>
</tr>
<tr>
<td>3-4 months</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Eculizumab</td>
</tr>
<tr>
<td>P-value</td>
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</tbody>
</table>

*Residual DSA was not removed after the transplant
AMR: C1 Esterase Inhibitor Mechanistically Attractive Due To Proximal Complement Blockade\(^1\)

FDA approved for HAE: Hereditary Angioedema

C1-INH: C1 esterase inhibitor; FDP: fibrin degradation product; HMWK: high molecular weight kininogen; iC: intercellular; KK: kallikrein; MASP: MBP-associated serine protease; MBP: mannose-binding protein; TNF: tumor necrosis factor; tPA: tissue plasminogen activator


AMR: Randomized Placebo Controlled C1 INH Trial Cg on 6 mos. Biopsy\(^1\)

This study was sponsored by ViroPharma, Inc., a wholly owned subsidiary of Shire, PLC.

CG = chronic glomerulopathy 17 mg/dL = 1 U/mL


C1-INH (Berinert) as add on Therapy for Chronic AMR Unresponsive to SOC\(^1\)

\(^1\)Viglietti et al. Am J Transplant;16:1596
**IdeS:** IgG-degrading enzyme of *Streptococcus pyogenes*

Highly specific for human IgG

*Single-cleaved IgG (sclgG)*

\[ \text{IgG} \rightarrow \text{sclgG} \rightarrow \text{Fc} \]

1st

2 hrs

2nd

4 hrs

**Trouble in paradise:** IgG rebounds by day 14 and patient cannot be given more than 2 doses because of antibody formation

**IdeS Effect on Class II Antibody In A Sensitized Patient**

**HLA Incompatible Donor IdeS Protocol**
Which of the following best describes you?

1. I know there are no effective treatments for chronic AMR so I just let nature take its course and begin to plan for the next transplant.
2. When I identify a patient with chronic AMR I increase maintenance immunosuppression and observe.
3. I aggressively treat chronic AMR when found on a for cause biopsy.
4. I monitor at risk patients with protocol biopsies and treat chronic AMR until the microcirculation inflammation resolves on re-biopsy.

Which of the following is false about the treatment of chronic AMR

A. Therapies for Acute AMR tend to have limited efficacy for chronic AMR.
B. Class I non-complement fixing antibodies are associated with the worst outcomes.
C. DSA that binds C1q leads to a higher rate of graft loss.
D. Transplant glomerulopathy can result from both acute and chronic AMR