New Developments in Desensitization Protocols: Is There a Standard of Care?

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Professor of Surgery
Director of the NYU Langone Transplant Institute
Disclosures:

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

Received consulting fees from OrbidMed, GuidePoint Global, Sucampo, Astellas, and Shire

Received research grants from Immune Tolerance Network, ViroPharma, Hansa, and Alexion.

Involved in clinical trial design for some of the off label drugs I will be discussing:

- anti-CD20
- IdeS
- C5 inhibitor
AMR Is Associated With A Poor Outcome\textsuperscript{1}

Compare Apples To Apples

• Outcomes of desensitization protocols need to be compared to options that are actually available to the patient

• For a patient with a CPRA of 100% receiving a compatible kidney has not been a realistic option and this should not be the reference intervention
Survival Advantage of Desensitization Over Remaining on the Waitlist\textsuperscript{1}

### DSA Fate By Specificity After Plasmapheresis

<table>
<thead>
<tr>
<th>Specific</th>
<th>Eliminated</th>
<th>Persistent</th>
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</thead>
<tbody>
<tr>
<td>cl</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>
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</table>

Graft survival is related to DSA strength.
Risk Of AMR In Desensitized Patients By HLA DSA Strength

323 HLAi Txs From 2/98-1/14

- Luminex+: MFI 2,000-5,000, 19.5%
- Flow+: MFI 5,000-10,000, 20.5%
- CDC+: MFI >10,000, 34.5%

1Montgomery RA et al. unpublished.
Marked Survival Advantage of Desensitization vs. Other Available Options Even At CDC+ Strength

Combining Paired Donation With Desensitization

Point Changes: Sensitization

CPRA Sliding Scale (Allocation Points) (CPRA<98%)

CPRA

Points

0 0 0 0 0.08 0.21 0.34 0.48 0.81 1.09 1.58 2.46

0 2 4 6 8 10 12 14 16 18 20

0 10 20 30 40 50 60 70 80 90 100

Pre KAS

Post KAS
CPRA 99-100% recipient “≈2 yrs bolus effect”

Transplants to CPRA 99-100% rose sharply after KAS; tapered to 10%

SRTR
KAS Priority For Highly Sensitized Candidates: Hopkins Data

- Current Waiting list (active & inactive): 1338 patients
- CPRA 98-100%: 164 candidates (12%)
- Since new KAS: CPRA ≥ 98%
  - DDRT 66 patients transplanted
  - 64/66 of them had CPRA 100%
  - LDRT HLA incompatible 25 patients (normally > 50)
Competition For The Same Rare Genotypes Results In A Low KPD Match Rate\(^1\)

Plasmapheresis Based SOC Desensitization for HLAi LD Recipients

**Steroids**
- ATG
- Anti-CD20*

- FK506 (0.1 mg/kg/d)
- MMF (2 gm/d)

Preoperative PP/IVIG

Stay PK

Postoperative PP/IVIG

Continue FK506
Continue MMF (2 gm/d)
Prednisone Taper

TXP

Goal is a (−) Cyto XM


Goal is a (−) Flow XM

*For repeat mismatches and CDC+XM*
Does Rituximab Prevent An Anamnestic Response¹

<table>
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<tr>
<th>Made Antibody to Tetraser Antigenᵇ</th>
<th>Treated With Rituximab</th>
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<tr>
<td></td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Yes</td>
<td>0</td>
<td>13</td>
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<tr>
<td>No</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

\[X^2_1 = 16.2\]
\[P = .00006\]

- Tetraramers used to determine the frequencies of B cells with HLA specificities that are not producing soluble antibody
- Tetraramers are available only for a limited number of HLA molecules

¹ There was not detectable antibody to the tested tetraramer antigen prior to transplantation. ᵇ Made antibody to the tetraramer antigen after transplantation.

Rituximab and Intravenous Immune Globulin for Desensitization during Renal Transplantation

Ashley A. Vo, Pharm.D., Marina Lukovsky, Pharm.D., Mieko Toyoda, Ph.D., Jennifer Wang, M.D., Nancy L. Reinsmoen, Ph.D., Chih-Hung Lai, Ph.D., Alice Peng, M.D., Rafael Villicana, M.D., and Stanley C. Jordan, M.D.

80% Transplant rate and 94% graft survival
Outcomes of IVIg Desensitization With and Without Anti-CD20

Kaplan-Meier Graft Survival in Patients Desensitized with IVIG vs. IVIG + Rituximab

Log Rank p=0.0042

Vo et al. ATC 2013 Abstract #841

Courtesy of S. Jordan
## Therapies and Intervention For HLA DSA

<table>
<thead>
<tr>
<th>The Tackle Box</th>
<th>Standard of Care (SOC)</th>
<th>Add-ons to SOC</th>
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<tr>
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<tr>
<td></td>
<td>Plasmapheresis</td>
<td>Anti-CD20</td>
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<tr>
<td></td>
<td>Immunoabsorption</td>
<td>Complement Inhibitors (eculizumab and C1INH)</td>
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<td>IVIg (high or low dose)</td>
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<tr>
<td></td>
<td>Steroids or ATG</td>
<td>Proteosomal Inhibitors</td>
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<td></td>
<td>[Rituximab]</td>
<td>Tocilizumab (anti-IL-6R)</td>
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<td></td>
<td>Splenectomy</td>
<td>IdeS</td>
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<td></td>
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<td>Splenic Irradiation</td>
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</table>
Classical Complement Pathway in Acute AMR in Sensitized KTRs

ECULIZUMAB

**a** FDA approved for PNH and aHUS.

AMR, antibody-mediated rejection; DAF, decay-accelerating factor; DSAs, donor-specific antibodies; HLA, human leukocyte antigen; Y-CVF, Yunnan-cobra venom factor.

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

L. D. Cornell¹, C. A. Schinstock², M. J. Gandhi³, W. K. Kremers² and M. D. Stegall²,*

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>
<th>3-4 months</th>
<th>1 year</th>
<th>2 years</th>
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<tbody>
<tr>
<td>Eculizumab*</td>
<td>0% (0/28)</td>
<td>26.7%  (8/30)</td>
<td>45.4%  (10/22)</td>
</tr>
<tr>
<td>Control</td>
<td>9.3% (4/43)</td>
<td>39.5%  (15/38)</td>
<td>63.6%  (21/33)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.15</td>
<td>0.31</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*Residual DSA was not removed after the transplant
IdeS characteristics in humans

- IdeS treatment inhibits Fc-mediated activities
  - IgG mediated CDC
  - IgG mediated ADCC
  - IgG mediated phagocytosis
- IdeS only cleaves IgG (not IgM, IgA, IgD or IgE)
- IdeS has selective species specificity (human & rabbit)
- IdeS cleaves all forms of IgG: free, bound to antigen and membrane bound (BCR)
- PK of IdeS
  - Alpha phase (distribution): 5 h
  - Beta phase (elimination): 70 h
- IdeS is immunogenic and not novel to the immune system
IdeS: IgG-degrading enzyme of *Streptococcus pyogenes*

*Highly specific for human IgG*

\[
(ab')_2
\]

\[
\text{Glu-Leu-Leu-Gly}_{236}\text{ G\text{ly-Pro}}
\]

\[
2 \text{ hrs} \quad \text{4 hrs}
\]

*Single-cleaved IgG (sclIgG)*
IdeS Effect on Class I Antibody In A Sensitized Patient
IdeS Effect on Class II Antibody In A Sensitized Patient

Trouble in paradise: IgG rebounds by day 14 and patient cannot be given more than 2 doses because of antibody formation.
HLA Incompatible Donor IdeS Protocol

Positive Cytotoxic or Flow XM

- XM

IdeS .24 mg/kg

2 hrs

Solumedrol 500mg/d

Tx

d 0

Campath SQ

d 4

IVlg 2 gm/kg

d 7

Anti-CD2

d 9

SOC rescue If needed

IdeS .24 mg/kg If XM still +
**IdeS Desensitization: NYU Patient #2**

<table>
<thead>
<tr>
<th>DONOR FLOW CROSSMATCH</th>
<th>Flow Cytometry</th>
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<tbody>
<tr>
<td></td>
<td>Recipient Untreated Serum</td>
</tr>
<tr>
<td></td>
<td>4/6/2017</td>
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<tr>
<td>Donor B Cell</td>
<td>Pos (275)</td>
</tr>
<tr>
<td>Donor T Cell</td>
<td>Pos (264)</td>
</tr>
</tbody>
</table>

45 yo patient with 20 years on HD and 100% CPRA. We eliminated as unacceptable all HLA ab with MFI < 20,000 and she still had a 100% CPRA. Received an import offer for a 41 yo DBD with a + CDC XM.
### Pre-IdeS

<table>
<thead>
<tr>
<th>RELATION</th>
<th>ABO</th>
<th>A</th>
<th>B</th>
<th>Bw</th>
<th>C</th>
<th>DR</th>
<th>DR</th>
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<th>DP</th>
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Peak MFI Values:
- SELF: 24,103
- DECEASED: 23,721, 5,985

**HLA Typing**

Typing results are the most probable serological equivalents for low/intermediate molecular (DNA) testing. NT: Not typed for the HLA locus.

A serum is scored POSITIVE for an antigen if the MFI value is greater than or equal to 2000.

### 2 hr Post-IdeS

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</table>

Peak MFI Values:
- SELF: 10,271
- DECEASED: 7,736, 662, 5,530, 4,532

**HLA Typing**

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### 48 hrs Post-IdeS

**HLA Typing**

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<th>B1</th>
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<th>B4</th>
<th>DR B5</th>
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**Peak MFI Values**

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<tr>
<th>RELATION</th>
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*Peak MFI Values: 3,318 and 2,092*

**A serum is scored POSITIVE for an antigen if the MFI value is greater than or equal to 2000.**

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### 5 days Post-IdeS

**HLA Typing**

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**Peak MFI Values: 2,092**

**A serum is scored POSITIVE for an antigen if the MFI value is greater than or equal to 2000.**
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