Highly Sensitized Transplant Candidate

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FDA WORKSHOP:
ANTIBODY MEDIATED REJECTION
IN KIDNEY TRANSPLANTATION

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Disclosure

• Funding:
  – BMS- *Investigator Initiated Trial*
  – Takeda Millennium- *Investigator Initiated Trial*
  – NIDDK- *R01*

• Off label drug use
  – The of material in this presentation WILL include discussion of unapproved or investigational uses of products.
Highly Sensitized Transplant Candidate

- Background
- Clinical Studies
- Outcomes
- Limitations
- Future Directions
Growing numbers: ~14,000 patients in 2015

Modest impact of new KAS on total rate of transplant

Accumulation of highly sensitized transplant candidates on the waitlist

New KAS has modest impact on total rate of transplantation in highly sensitized

The Problem: IgG

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IVIG decreases sensitization

The NIH IG02 Trial

RCT of sensitized patients (n=98) to IVIG 2g/kg/m x 4 vs. placebo

Decline in PRA was significant but transient (6M)

IVIG associated with better transplantation rate

-starting PRA less than 80%

The effect was transient (6M)

p < 0.05

35% vs. 17%

Mechanisms of action of IVIG

Schwab et al, Nat Rev Immunol, 2013
Rituximab and High Dose IVIG

Successful Desensitization

Panel-Reactive Antibody (PRA)

- Before First Infusion: 77±18%
- After Second Infusion: 44±30%

T-Cell Flow-Cytometric Mean Channel Shift

- Before Treatment
- After Treatment
- Before Transplantation

N=20

IVIG 2 g/kg
- Day 1

Rituximab 1 g
- Day 7

Rituximab 1 g
- Day 22

IVIG 2 g/kg
- Day 30

Tx = 16
- 10 LD
- 6 DD

Pretransplant desensitization with IVIG and rituximab was not successful in highly sensitized kidney transplant candidates with cPRA > 90%.
Rituximab induction

Reduced incidence and magnitude of HLA antibody rebound

Rituximab reduced antibody strength and rebound

No difference in DSA elimination, AMR, and 5 year graft survival

PLEX and low-dose IVIG in live donor Kidney Recipients

Desensitization treatment (n=211, cPRA 82% ± 23)

Dialysis or transplantation

Dialysis only

Patient Survival, %

0 10 20 30 40 50 60 70 80 90 100

0 12 24 36 48 60 72 84 96

Months

Day -10

TAC/MPA

PP/IVIG

ATG or IL2-B

Tx

Day 0

PP/IVIG

Day +8

PP/IVIG

PP/IVIG

PP/IVIG

Proteasome Inhibitor-Based Desensitization

Was relatively successful in live and deceased donor Tx

Intent to treat 52 patients → Completed 38 (73%) → 19 transplanted (37%)

cPRA$_{1500}$ 91%

Tabalumab (BAFF inhibitor) had Minimal Effect in Highly Sensitized

Tabalumab (anti-BAFF), at doses of 240-mg subcutaneous (SC) at Week 0 followed by 120-mg SC monthly for 5 additional months (Baseline cPRA 94.4±9.1%, n=18 -> 3 transplanted )
Desensitization with **Eculizumab**

*Short term success but limited outcome beyond 1 year*

Eculizumab did not prevent cABMR at 2 yrs

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# Summary of clinical studies

**Limited impact on PRA and transplant rates**

<table>
<thead>
<tr>
<th>PI</th>
<th>N</th>
<th>c/PRA</th>
<th>Regimen</th>
<th>Effect PRA</th>
<th>Transplant</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jordan</td>
<td>98</td>
<td>~70%</td>
<td>IVIG</td>
<td>~5%</td>
<td>35% v. 17%</td>
</tr>
<tr>
<td>2</td>
<td>Vo</td>
<td>20</td>
<td>77%</td>
<td>-</td>
<td>(-) 33%</td>
<td>16 (80%)</td>
</tr>
<tr>
<td>3</td>
<td>Lobashevski</td>
<td>31</td>
<td>65-100%</td>
<td>IVIG-Ritux</td>
<td>-</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>4</td>
<td>Marfo</td>
<td>13</td>
<td>&gt;90%</td>
<td>-</td>
<td>-</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>5</td>
<td>Alachkar</td>
<td>27</td>
<td>100%</td>
<td>-</td>
<td>-</td>
<td>11 (41%)</td>
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<tr>
<td>6</td>
<td>Stegall</td>
<td>26</td>
<td>N/A</td>
<td>Eculizumab</td>
<td>N/A</td>
<td>26 (100%)</td>
</tr>
<tr>
<td>7</td>
<td>Woodle</td>
<td>52</td>
<td>91%</td>
<td>Bortez-Ritux-PLEX</td>
<td>25% responders</td>
<td>19 (37%)</td>
</tr>
<tr>
<td>8</td>
<td>Mujtaba</td>
<td>18</td>
<td>94%</td>
<td>Tabalumab (BAFF)</td>
<td>±</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>9</td>
<td>Vo</td>
<td>10</td>
<td>74% (I)</td>
<td>93% (II)</td>
<td>IVIG-Tocilizumab (IL6-R)</td>
<td>(-) 15% (I)</td>
</tr>
<tr>
<td>10</td>
<td>Naji</td>
<td>8</td>
<td>N/A</td>
<td>Belimumab (BAFF)</td>
<td>-</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>11</td>
<td>Redfield</td>
<td>24</td>
<td>N/A</td>
<td>IVIG-Obinutuzumab (CD20)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>12</td>
<td>Woodle</td>
<td>8</td>
<td>N/A</td>
<td>Carfilzomib (PI)</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>13</td>
<td>Jordan</td>
<td>15</td>
<td>N/A</td>
<td>Ides (IgG endopeptidase)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Quantifying the risk of incompatible kidney transplantation: a multicenter study

Orandi et al, American Journal of Transplantation 2014; 14: 1573–1580

PCC, positive cytotoxic crossmatch; PFNC, positive flow, negative cytotoxic crossmatch; PLNF, positive Luminex, negative flow crossmatch

Orandi et al, American Journal of Transplantation 2014; 14: 1573–1580
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Considering **Non-HLA antigens**

1. High PRA associated with poor graft survival in HLA-identical sibling transplants

   ![Graph showing graft survival](image)

   - No PRA
   - 1-50% PRA
   - >50% PRA

   Number of transplants:
   - No PRA: 3001
   - 1-50% PRA: 803
   - >50% PRA: 244

2. AT1R mediated Rejection

   - Losartan + PLEX

   ![Graph showing graft survival](image)

   - Untreated
   - Treated

   Patients at Risk:
   - Untreated: 7, 5, 4, 4
   - Treated: 9, 3, 2, 2

3. Endoglin Fms-like tyrosine kinase-3 (FLT3) ligand

   ![Images of Endoglin](image)

4. Overview of non-HLA antibodies directed against endothelial targets

   ![Diagram of endothelial targets](image)

References:
1. Opelz et al, Lancet 2005
Targeting B cell Development

Targeting B cell Activation

BAFF, APRIL and their Receptors

Myeloid or stromal cell

Membrane-bound BAFF
Soluble BAFF

BAFF

BAFF-R

B cell

Myeloid or stromal cell

HSPG-bound APRIL
Soluble APRIL

APRIL

TACI

BCMA

- Transitional B cell survival and maturation
- Sustains GC reaction and supports Ig isotype switching
- T-cell-independent antibody responses
- Supports Ig isotype switching
- Negative regulator of B cell compartment size
- Plasma cell survival

Targeting Bone Marrow

*Plasma Cells and their Survival Niche*

<table>
<thead>
<tr>
<th></th>
<th>Naïve B cell</th>
<th>Plasmablast</th>
<th>Mature Plasma Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifespan</td>
<td>++</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Proliferation</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>CD (27, 38, 138), CXCR4</td>
<td>-</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>CD (19, 20, 45), MHCII</td>
<td>+++</td>
<td>++</td>
<td>±</td>
</tr>
<tr>
<td>Location</td>
<td>L.O.</td>
<td>Blood, L.O.</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>Isotype</td>
<td>IgM, IgD</td>
<td>All</td>
<td>IgG&gt;&gt;IgA&gt;IgM</td>
</tr>
<tr>
<td>BLIMP1</td>
<td>-</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

The important role of the *Stromal* cell

Nutt et al, Nat Rev Immunol 2015
Finding the right **combination** therapy

- **CD20** (Rituximab, Obinutuzumab)
- **APRIL** (Atacicept)
- **BAFF** (Belimumab, Tabalumab)
- **Proteasome**
- **IL6** (Tocilizumab)
- **CD138** (Indatuximab Ravtansine)
- **CD38** (Isatuximab, Daratumumab)
- **PLEX**
- **Ides** (IgG endopeptidase)
- **Eculizumab**
- **C1 esterase inhibitor**

**IVIG**

**Endothelial cell**

**APC** (macrophages, dendritic cells)

**T cell**

**B cell**

**Plasma cell**

**Complement**

- **Pulse steroids**
- **Thymoglobulin**
- **Belatacept**
- **Calcineurin inhibitors**

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Kidney Paired Donation (KPD)

Combining DSZ + KPD

Desensitization

KPD

Pham et al, Transplantation Reviews 2017
Summary and Future Directions

- Desensitization of highly sensitized possible but with **limited** and **transient** impact on antibody (PRA) levels
- Need to better understand the **pathogenesis** of sensitization
- Define **combination** therapies
  - KPD ± desensitization
  - Targeting up- and downstream pathways of B cell activation
- Determine efficacy **endpoints** for clinical trials
  - cPRA and def. of antibody strength for unacceptable Ag?
  - Transplantation?
  - Immunodominant antibody?
  - Non-HLA antibodies?
Thank you!

- CD20 (Rituximab, Obinutuzumab)
- APRIL (Atacicept)
- BAFF (Belimumab, Tabalumab)
- Proteasome
- IL6 (Tocilizumab)
- CD138 (Indatuximab, Daratumumab)
- PLEX
- Ides (IgG endopeptidase)
- Pulse steroids
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