Unmet Needs in Kidney Transplantation: Desensitization

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Objectives:
- Discuss current desensitization therapies as a means to improve transplantation for highly-HLA sensitized patients.
- Discuss clinically relevant end points that allow successful transplantation to occur.
- Discuss potential surrogate end points for studies that could benefit adult and pediatric patients.
- Discuss unmet needs in desensitization for adult and pediatric patients.
• The purpose of DES therapy is to accomplish antibody reduction to an acceptable level that allows for successful transplant.

• **Complete elimination of all DSAs in not required and not desirable** as excessive reductions in total IgG would be likely exposing the patients to increased infection risk.
Case Report: CC is a 2.5 y.o. Asian female with ESRD secondary to congenital obstructive uropathy. Patient had 1 failed DD transplant at age 1 y.o. and became sensitized. Mother came forward as a potential donor, but work up revealed the following: DSA: B60 strong, C10 moderate DR12,DQ7, DR52 weak to moderate. DSA RIS score was 21. FCMX was T-200 CS, B-352 CS.

What would you do?
- Have child remain on dialysis?
- Paired exchange?
- Attempt desensitization?
Patient underwent desensitization with IVIG + Rituximab without successful reduction of DSAs. After 6M, the patient received PLEX +IVIG/Rituximab and was transplanted with DSA: 200, BCMX 283. Patient received induction with Campath 1H and maintained on Pred/Tacro/MMF.

At 1M post-transplant, the only DSA present was a weak DQ7. DSAs have subsequently disappeared. Patient is now 5.5 years post-transplant with SCr 0.9mg/dl. Biopsy in 2014 showed no evidence of ABMR or TG. Patient now in second grade doing well!
Measuring Efficacy of Desensitization

: The NIH IG02 Study

Graphs showing PRA percent over study months for IgM + IgG and IgG only, comparing IVIG and placebo treatments.
Rituximab and Intravenous Immune Globulin for Desensitization during Renal Transplantation

Ashley A. Vo, Pharm.D., Marita Lukovský, Pharm.D., Makio Taya, Ph.D., Jennifer Wang, M.D., Nancy L. Roncione, Ph.D., Chih-Hung Lai, Ph.D., Alice Peng, M.D., Rafael Villicana, M.D., and Stanley C. Jordan, M.D.

ABSTRACT

BACKGROUND
Few options for transplantation currently exist for patients highly sensitized to HLA. This exploratory, open-label, phase 1-2, single-center study examined whether intravenous immune globulin plus rituximab could reduce anti-HLA antibody levels and improve transplantation rates.

METHODS
Between September 2005 and May 2007, a total of 30 highly sensitized patients (with a mean ±SD) T-cell panel-reactive antibody level, determined by the use of the complement-dependent cytotoxicity assay, of 77±10% or with donor-specific antibodies were enrolled and received treatment with intravenous immune globulin and rituximab. We recorded rates of transplantation, panel-reactive antibody levels, cross-matching results at the time of transplantation, survival of patients and grafts, acute rejection episodes, serum creatinine values, adverse events and serious adverse events and immunosuppressive factors.

http://online.wsj.com/article/SB121623403383459229.html
Desensitization Protocols: Cedars-Sinai Medical Center

UNET Listed DSA Avoids:
- All C1Q+ Antibodies
- Antibodies >10,000 MFI

2 wks

IVIG → Rituximab → IVIG

2 wks

CMX Acceptable
Repeat in 6M if no Tx

CMX Unacceptable
Live
PP x 5-7

IVIG + Anti-IL6R

Transplant

Frequent Offers

Transplant Immunotherapy Program
Unmet Needs in Kidney Transplantation: Desensitization

Data From HS-Pediatric Transplant Patients at Cedars-Sinai
**DSA RIS Trends of HS Pediatrics Patients (N=16)**

*Relative Intensity Scale (RIS) [0 points = No DSA; 2 points = <5000MFI {weak}; 5 points = 5000-10,000 MFI {moderate}; 10 points = >10,000MFI {strong}].*
Average DSA RIS score of Pediatric HS Patients  (N= 16)

*Relative Intensity Scale (RIS) [0 points = No DSA; 2 points = <5000MFI {weak}; 5 points = 5000-10,000 MFI {moderate}; 10 points = >10,000MFI {strong}].

p = 0.0088

p = 0.029

p = 0.0088
Figure 1: Kaplan-Meier curves out to 1 year post-transplant. Figure A demonstrates no difference in graft loss between HS patients who received alemtuzumab, compared to non-sensitized patients receiving anti-IL-2R induction. Figure B shows a statistically significant increase in graft rejection in HS group receiving alemtuzumab compared to non-sensitized pediatric patients receiving anti-IL-2R induction.
Freedom from ABMR Highly Sensitized (HS) vs Non-HS Pediatric Patients

Non HS (3 of 36 = 8% with ABMR)

HS (4 of 16 = 25% with ABMR)

P = 0.104
Freedom from BK Viremia by Sensitization Status

Group A: Peds HS
Group B: Peds NonHS

p = 0.97
Freedom from CMV by Sensitization Status

- Group A: Peds HS
- Group B: Peds NonHS

p = 0.77

Years Post Transplant:

- 0
- 0.5
- 1.0
- 1.5
- 2.0
- 2.5
- 3.0

Percent Free from CMV Viremia:

- 0.25
- 0.5
- 0.75
- 1.0
Renal Function in HS- v. HS+ Patients Transplanted After Desensitization

Mean SCr (mg/dl)

Time (months)

0M

6M

12M

24M

P=NS

HS+

HS-
• Aims:
The aim of our study was to establish an algorithm for assignment of unacceptable antigens (UAs) such that a complement dependent cytotoxicity crossmatch (CDC-XM) would be **negative** and a concomitant flow cytometric crossmatch (FXM) would be **weakly positive** (<225 CS) to allow for successful transplant of sensitized kidney recipients.
Desensitization with IVIG + Rituximab is Effective in Improving DD Transplant Rates for HS Patients with CPRA >80%

<table>
<thead>
<tr>
<th></th>
<th>Total Treated</th>
<th>Total Transplanted</th>
<th>Predicted UNOS Transplant Rates</th>
<th>Rates of Allograft Rejection</th>
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<tbody>
<tr>
<td>Totals</td>
<td>230</td>
<td>143 (62%)</td>
<td>6.5%†</td>
<td>35 (24.4%)</td>
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<tr>
<td>FCMX+ @ Transplant</td>
<td>66 (46%)</td>
<td></td>
<td></td>
<td>AMR+23 (16%) AMR-43 (30%)</td>
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<td>FCMX- @ Transplant</td>
<td>63 (44%)</td>
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<td>CMR+10 (7%) AMR+1 (0.5%) AMR-/CMR-51 (36%)</td>
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<tr>
<td>0 Mismatched @ Transplant</td>
<td>14 (10%)</td>
<td></td>
<td></td>
<td>AMR+1 (0.5%)</td>
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Total treated: n=230. CPRA, calculated panel reactive antibody; AMR, antibody-mediated rejection; CMR, cell mediated rejection. Note, transplant rates for patients with CPRAs >80% are 6.5%/year (Montgomery et al., 2011b)†.

*Discovery Medicine, Volume 13, Number 71, April 2012*
Navigating Donor Antibodies for Best Outcomes

345 DD Transplants

194 No DSAs

151 + DSAs Desensitized

20 Zero MM (Excluded)

131 No C1q+DSAs Negative CDC+

110 ABMR (-) (84%)

21 ABMR (+) (16%)
Factors Predicting Risk for Antibody-mediated Rejection and Graft Loss in Highly Human Leukocyte Antigen Sensitized Patients Transplanted After Desensitization

Ashley A. Vo,1 Aditi Sinha,2 Mark Haas,3 Jua Choi,1 James Mirocha,4 Joseph Kahwaji,1 Alice Peng,1 Rafael Villicana,1 and Stanley C. Jordan1

Background. Desensitization with intravenous immunoglobulin and rituximab (I+R) significantly improves transplant rates in highly sensitized patients, but antibody-mediated rejection (ABMR) remains a concern. Patients and Methods. Between July 2006 and December 2012, 226 highly sensitized patients received transplants after desensitization. Most received alemtuzumab induction and standard immunosuppression. Two groups were examined: ABMR− (n = 181) and ABMR+ (n = 45, 20%). Risk factors for ABMR, pathology, and outcomes were assessed. Results. Significant risks for ABMR included previous transplants and pregnancies as sensitizing events, donor-specific antibody (DSA) relative intensity scores greater than 17, presence of both class I and II DSAs at transplant and time on waitlist. The ABMR+ showed a significant benefit for graft survival and glomerular filtration rate at 5 years (P < 0.0001). Banff pathology characteristics for ABMR+ patients with or without graft loss did not differ. C4d+ versus C4d− ABMR did not predict graft loss (P = 0.086). Thrombotic microangiopathy (TMA+) significantly predicted graft failure (P = 0.045). The ABMR episodes were treated with I+R (n = 25), or, in more severe ABMR+, plasma exchange (PLEX)+I+R (n = 20). Graft survival for patients treated with I+R was superior (P = 0.028). Increased mortality was seen in ABMR+ patients experiencing graft loss after ABMR treatment (P = 0.004). The PLEX + Eculizumab improved graft survival for TMA+ patients (P = 0.036). Conclusion. Patients desensitized with I+R who remain ABMR− have long-term graft and patient survival. The ABMR+ patients have significantly reduced graft survival and glomerular filtration rate at 5 years, especially TMA+. Severe ABMR+ episodes benefit from treatment with PLEX + Eculizumab. The DSA-relative intensity scores at transplant was a strong predictor
Risk for ABMR after Desensitization

DSA Number & Strength are Strong Predictors of Risk for ABMR

Vo et al Transplantation 2014
Factors Predicting Risk for ABMR and Graft Loss in Highly HLA-Sensitized Patients Transplanted After Desensitization

Death Censored Graft Survival by ABMR Status

Death Censored Graft Survival by Treatment Status for ABMR

Patient Survival by Graft Loss Status After ABMR Treatment

ABMR is associated with high risk for allograft loss and death

* IVIG + rituximab. † PLEX + IVIG + rituximab.
Impact of Desensitization on SRTR Outcomes

Post-Transplant Allograft Survival by CMX Status at Transplant

Number at risk

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<tr>
<th>Group</th>
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<td>164</td>
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<td>8215</td>
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Orandi, BJ AJT 2014;14: 1573-80
Post-Transplant Mortality by CMX Status at Transplant after Desensitization

Orandi, BJ AJT 2014;14: 1573-80
Outcomes of Desensitization & Transplantation Compared with Dialysis

Effect of IVIG + Rituximab on Wait-Time to Transplantation for Highly-HLA Sensitized Patients
Outcomes of Desensitization & Transplantation Compared with Dialysis

Patient Survival After Desensitization & Transplant for Patients with PRA>80%

Transplant Immunotherapy Program
Graft Survival After Desensitization & Transplant for Patients with PRA>80%

Living Donor

Deceased Donor

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<tr>
<th>Time (mo)</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
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<td>23</td>
<td>18</td>
<td>12</td>
<td>6</td>
<td>3</td>
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<tr>
<td>Number (DD)</td>
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<td>85</td>
<td>70</td>
<td>58</td>
<td>47</td>
<td>36</td>
<td>21</td>
<td>15</td>
<td>14</td>
<td>7</td>
<td>3</td>
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</table>
Outcomes of Desensitization & Transplantation Compared with Dialysis

Highly-HLA Sensitized Patient Survival by Treatment Type: Dialysis v. Desensitization & Transplantation

Transplant Immunotherapy Program
Outcomes of Desensitization & Transplantation Compared with Dialysis

No. at Risk

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<th>Desensitization treatment</th>
<th>Dialysis or transplantation</th>
<th>Dialysis only</th>
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<tr>
<td>No.</td>
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<td>170</td>
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<td>Dual therapy</td>
<td>1027</td>
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<tr>
<td>Dialysis only</td>
<td>1012</td>
<td>822</td>
<td>626</td>
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Montgomery et al NEJM 2012

Transplant Immunotherapy Program
Outcomes of Desensitization & Transplantation: IVIG or IVIG + Rituximab

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

Log Rank p=0.0042

IVIG + Rituximab

IVIG Alone

Follow Up (Months)

IVIG Alone: N=30

IVIG + Rituximab: N=117

Vo et al. ATC 2013 Abstract #841
Course of DSAs Pre- & Post-Transplant in IVIG + Placebo

Figure 2A
Outcomes of Desensitization & Transplantation: IVIG or IVIG + Rituximab

Course of DSAs Pre- & Post-Transplant in IVIG + Rituximab

Figure 2B
Total Desensitized Patients

1 dose of Rituximab
N= 397

2 doses of Rituximab
N= 91

3 doses of Rituximab
N=22

4 doses or more Rituximab
4 doses: N = 3
5 doses: N = 1

Transplanted N= 414
(80.5%)

Not Transplanted N= 101
Expired: 10
Delisted: 16
Waitlisted: 75
Desensitization combined with avoidance of C1q+ DSAs can be quite successful with ABMR rates ~ 20% and graft survival rates comparable to non-sensitized patients.

Patient survival is quite superior for patients desensitized and transplanted v. those HS patients remaining on dialysis.

Current DSA monitoring techniques are problematic in that efficacy of desensitization cannot be discerned by assessment of CPRA values. Cellular assays are essential before proceeding to transplantation.

Pediatric desensitization appears to yield results and outcomes similar to that for adults.
Unmet Needs in Desensitization

• A recognition by SRTR that centers performing desensitization are serving a higher risk population than non-sensitized patients and appropriate risk adjustments should be granted.

• Need for increased biotech & transplant center collaboration to improve implementation of novel therapies aimed at modifying antibodies, B-cells, plasma cells and complement.

• Current DSA monitoring techniques are problematic in that efficacy of desensitization cannot be discerned by assessment of CPRA values. Cellular assays are essential before proceeding to transplantation. Need for innovative thinking here.

• Pediatric patients represent a growing and underserved population of sensitized patients and should be included in clinical trials.
Thanks for your attention!