Strategies for Desensitization

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BC Nephrology Day October 8th 2010
Pre-transplant crossmatch (CMX) with donor lymphocytes has been standard of practice

Positive CDC CXM $\rightarrow$ contraindication to transplant

Modifications to CXM $\rightarrow$ increased transplant success rates but relegated increased number of patients to longer waiting times
Sensitization Increases Median Waiting Time

- In U.S. 30% of patients on waiting list are sensitized (transfusion, pregnancy, transplant)
- 6.5% of highly sensitized patients (PRA >80%) receive a transplant per year

US Renal Data System Annual Data Report 2008
OPTN. Scientific Registry of Transplant Patients
Living Donor Paired Exchange (LDPE) Desensitization
Donor Specific Antibody

<table>
<thead>
<tr>
<th>Panel Reactive Antigen</th>
<th>Low DSA</th>
<th>High DSA</th>
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<tr>
<td>Low PRA</td>
<td>Easy for LDPE and Desensitization</td>
<td>Difficult for Desensitization</td>
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<td>O Donor</td>
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<tr>
<td>High PRA</td>
<td>LDPE $\rightarrow$ Desensitization</td>
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<td>AB Donor</td>
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Adapted from Segev et al TTS 2010
Definitions

- Desensitization

- ABO Incompatible Kidney Transplant

- Preparation of the Highly Sensitized Patient for Kidney Transplantation
Living Donor Transplant:
Attenuate the humoral alloimmune response so recipient becomes crossmatch negative against a specific donor

Deceased Donor Transplant:
Attenuate the humoral alloimmune response ($\Delta \%PRA$) making it more likely a recipient will receive a deceased donor transplant
General Approach to Desensitization

1. Remove or neutralize anti-IgG
2. Prevent formation of new anti-IgG before transplantation
3. Transplant when crossmatch (CMX) is negative
4. Prevent formation of new anti-IgG after transplantation
5. Rapidly diagnose and reverse acute AMR if it occurs
Desensitization Therapies

- High Dose IVIg
- Plasmapheresis
- Rituximab

Immunoadsorption
Desensitization worldwide

Immunadsorption

IVIG/PP

Immunadsorption/PP
Desensitization Therapies

- High Dose IVIg
- Plasmapheresis
- Rituximab

Immunoadsorption
Advantage of Protein A Column over Plasmapheresis: it only removes IgG

Tyden G. Transplant 2007, 84(s12): s27
Immunoadsorption (IA): Highly Sensitized

• **1996**: Kings College London\(^1\)
  – CXM + \(\rightarrow\) - with IA pre transplant but 70% AR and 53% graft survival at last follow up

• **1990-2003**: Vienna group\(^2\)
  – 40 highly sensitized patients \(\rightarrow\) IA pre and post deceased donor Tx + pre ATG x 10-14d
  – 73% 3-y survival graft survival; 20% cellular AR; 33% humoral AR

\(^1\)Higgins RM. Lancet 1996; 348:1208
\(^2\)Lorenz M. Transplantation 2005; 79:696
Common Desensitization Protocols in US

Cedars-Sinai

Mayo Clinic

Johns Hopkins
**Desensitization Therapies**

- **High Dose IVIg**
  - Pooled from multiple donors
  - Blocks Fc receptors on mononuclear phagocytes
  - Anti-idiotypic effects
  - Inhibits CD19 expression on activated B cells
  - Inhibits complement
  - Inhibits alloreactive T cells

- **Plasmapheresis**
  - Plasma separated from whole blood by filtration/centrifugation and discarded
  - Replacement of plasma with 5% albumin + isotonic saline/FFP
  - Removes anti-HLA antibodies
  - Immediately followed by low-dose IVIg

- **Rituximab**
  - Chimeric murine/human monoclonal Ab against CD20 Ag on surface of B cells
  - Not expressed on plasma cells
  - Prevents formation of new alloantibody-producing plasma cells
  - Inhibits B-cell driven Ag presentation and costimulation of T cells

**Immunoadsorption**
FIGURE 1. Plasma exchange. Plasma is separated from whole blood by filtration or centrifugation and then discarded. The whole plasma volume is replaced by Ringer’s solution and albumin and/or fresh-frozen plasma.
FIGURE 2. Double-filtration plasmapheresis. Plasma is separated from whole blood by filtration. The plasma is then passed through a second filter where substances with molecular weights of 170,000 (IgG) and 1,000,000 (IgM) are filtered out and discarded. Only the volume of the discarded immunoglobulin fraction is replaced by Ringer’s solution and albumin.
NIH IG02 Study
IVIg is superior to placebo in reducing anti-HLA Ab levels and improving transplantation rates in the highly sensitized

IVIg total dose not >180g
• 35% of IVIg v 17% placebo → transplant
• AR 9/17 IVIg; 1/10 placebo

Jordan SC. JASN 2004, 15:3256
Combining Rituximab and High Dose IVIg Reduces the Total Dose of IVIg

- PRA ↓ to 44% ± 30% (from 77% ± 19%)
- 16/20 transplanted; mean time to transplant = 5±6m
- AR = 50% (31% AMR); patient and graft survival at 1y = 100 and 97%

Vo AA, Jordan SC NEJM 2008, 359:242
Cedar-Sinai Protocol Using High Dose IVIg: Positive CMX Living Donor Desensitization

IVIg total dose not >140g

Jordan SC. CJASN 2006, 1:421
Cedar-Sinai Protocol Using High Dose IVIg:
Positive CMX Deceased Donor Desensitization

Jordan SC. CJASN 2006, 1:421
Cedar-Sinai Protocol Using High Dose IVIg + Rituximab in Highly Sensitized Patients Resistant to IVIg

If CMX is negative or acceptable T cell (flow CMX <250 channel shifts) → Transplantation
IVIg + Rituximab: Rejection and survival

• July 2006 - February 2009: 76 HLA-sensitized (HS) patients received KTX after desensitization using:
  – IVIG 2 g/kg (days 1 and 30)
  – Rituximab (1 g, day 15)
• 76 HS CMX+ treated patients (31 LD/45 DD) → TX
• Significant ↓ in T-cell flow CMXs from pretreatment to time of transplant.
• Time on wait list for DD recipients was ↓ from 95±6 months to 4.2±4.5 months after treatment.
• 37% → acute rejection (29% C4d+/8% C4d-).
• Patient and graft survival at 24 months = 95% and 84%.

Vo AA, Jordan SC. Transplant 2010, 89:1095
Johns Hopkins Protocol: CXM +

- If recipient begins with a positive AHG CDC crossmatch (+AHG XM) titer of 16.
- Average decrement of one dilution per PP/IVIg. 5 treatments → -AHG XM.
- In selective high-risk cases anti-CD20 given night before transplant.
- Induction includes an anti-IL2 blockade and high-dose steroids.
- Several posttransplant PP/IVIg treatments are performed by protocol.
- About 5% of +XM patients require rescue splenectomy for severe AMR.

Montgomery RA Am J Transplant 2010; 10:449
Mayo Clinic Protocol

Transplantation
Splenectomy
Thymoglobulin (1.5mg/kg x 10d)

Maintenance: (from POD 4)
Tacrolimus (target 12-16ng/ml)
MMF (1g/d) + prednisone

- Pre-operative Plasmapheresis and IV Ig (100mg/kg)
  day -4, -3, -1 and 0

- Post-operative Plasmapheresis and IV Ig (100mg/kg)
  day +1, and +3

- Anti-CD20 Rituximab (375mg/m²) POD 4

• N=14 + CXM to living donor
• AMR 29% but all reversible

Gloor JM. AmJTransplant 2003, 3:1017
Eurotransplant Algorithm Highly Sensitized

A

Deceased Donor Organ

PPh during organ transport
(2-2.5 x plasma exchange)

Cross Match 1 negative
(blood drawn before PPh)

Rituximab +
Basiliximab / Tacrolimus / EC-MPS / Methylprednisolone

Transplantation

Cross Match 1 positive
(blood drawn before PPh)

Cross Match 2 negative
(blood drawn after PPh)

No Transplantation

Cross Match 2 positive
(blood drawn after PPh)

Morath C Transplant 2010, 90:645
Eurotransplant Algorithm: Highly Sensitized

Living Donor Organ

6 x IA (2-2.5 x plasma exchange)
Tacrolimus / EC-MPS / Methylprednisolone

Cross Match 1 negative
(blood drawn before the 1st IA)
Rituximab + Basiliximab / Tacrolimus / EC-MPS / Methylprednisolone
Transplantation

Cross Match 1 positive
(blood drawn before the 1st IA)

Cross Match 2 negative
(blood drawn after the 5th IA)

No Transplantation

Cross Match 2 positive
(blood drawn after the 5th IA)

Morath C Transplant 2010, 90:645
High-Dose IVIg vs. PP + CMV-Ig

High-Dose IVIg
Advantages:
• Less expensive
• Success in living and deceased donor transplant
• Easy and safe (dialysis)
• Long-lasting desensitization in most cases

High-Dose IVIg
Disadvantages:
• Non- and incomplete responders (approx 10%)
• May interferes with DSA assays
• Antibody removal slower vs. PP + CMV-Ig
• Some IVIg products have toxicity (sucrose, saline)
• Fever, chills, H/A, anaphylaxis, thrombosis, nephrotoxicity (use isotonic)
<table>
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<tr>
<td><strong>PP + CMV-Ig</strong></td>
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<tr>
<td><strong>Advantages:</strong></td>
</tr>
<tr>
<td>• Highly effective</td>
</tr>
<tr>
<td>• Few non-responders</td>
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<tr>
<td>• DSA easy to follow</td>
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<tr>
<td>• Kinetics of DSA removal predictable</td>
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<tr>
<td>• Also removes anti-ABO-A or anti-ABO-B antibodies allowing potential transplantation across 2 incompatible barriers</td>
</tr>
<tr>
<td><strong>PP + CMV-Ig</strong></td>
</tr>
<tr>
<td><strong>Disadvantages:</strong></td>
</tr>
<tr>
<td>• Expensive</td>
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<tr>
<td>• Labor intensive</td>
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<tr>
<td>• Not useful if no living donor</td>
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<tr>
<td>• DSA can return post transplant</td>
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<tr>
<td>• Transplant must follow treatment or possible rebound</td>
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<tr>
<td>• Depletion of clotting factors, hypocalcemia, fever, chills</td>
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Definitions

Desensitization

ABO Incompatible Kidney Transplant

Preparation of the Highly Sensitized Patient for Kidney Transplantation
Johns Hopkins Protocol: ABO incompatible

- **Pre-op:** Alt day PP (COBE Spectra centrifuge-driven cell separator) → CMVIg (100mg/kg) and FK506 + MMF at time of 1st PP/CMVIg as per table
- Goal AHG titer ≤ 16 at time of Tx
- **Peri-op:** Steroids and daclizumab, hold FK506 am of surgery
- **Post-op:** FK506/MMF/steroids (wean to 20mg/d at d/c)
- Alt day PP/CMVIg as per table if titers fail to fall
- Protocol bx at 1, 3, 6, 12 months; 15%→ AHR; survival = other LRD Tx

Montgomery RA Transplantation 2009; 87(8):1246
Swedish Protocol: ABO Incompatible

- **Pre-op:** Rituximab (375mg/m2) d-30; Tac/MMF/Pred d-14
- Glucosorb IA d-6, -5, -2, -1 to target IgG titer <1:8 (if target titer not achieved 4 more IA over 1 w pre-op or IVIg (0.5g/kg) after last IA)
- **Post-op:** Glucosorb IA d 3, 6 and 9 with additional IA if titers >1:16
- Restricted to patients with titers <1:128
- 3-y outcomes equivalent to LRD; no ↑ AR

Genberg H Transplant 2008; 85:1745
Desensitization versus LDPE

Incompatible living donor

Positive crossmatch

Montgomery RA Am J Transplant 2010; 10:449
Desensitization versus LDPE

Montgomery RA Am J Transplant 2010; 10:449
Summary and Conclusion

• High dose IVIg, although slower to remove Abs, is an effective desensitization modality for both living and deceased donor transplantation.

• Combined PP + IVIg is highly effective for both HLA and ABO incompatibility but is expensive, time consuming and is not useful unless a transplant is imminent.

• Both protocols have favorable results in reducing transplant waiting time for highly sensitized ESRD patients

• For highly sensitized patients with a living donor: should try LDPE first and if fails then resort to desensitization. For highly sensitized patients with no donor → National Highly Sensitized Registry.
"BOY! TALK ABOUT ORGAN REJECTION!"
Johns Hopkins Protocol

- Splenectomy at transplantation in high risk or ABOi patients
- Superseded by antiCD20 (375mg/kg) night pre-transplant Segev DL AmJTransplant 2005, 5:2570

New Protocol: neither

Abstract # 1319 ATC, Boston 2009