The Utility of Protocol Biopsies in the Follow-up of Acute AMR and in the Detection of Chronic AMR

What do we know about histology and AMR clinically?

Tailored Immunosuppression Based on Routine DSA Monitoring (both in sensitized and nonsensitized patients)

Is there a standard of care regarding therapeutic management?

Mark D. Stegall MD
James C. Masson Professor of Surgery Research
Departments of Surgery and Immunology
Disclosures

• Ad Board—Novartis, Roche, Astellas
• Mayo Contract—Transplant Genomics, Inc.
• FDA—flight to DC and 1 night’s lodging
Goals of the Workshop:

1) Examine and emphasize the importance of immunosuppressive medication nonadherence in the development of de novo donor specific antibodies (DSA) and subsequent antibody mediated rejection (AMR)

- Agree, but not all patients are non-adherent
- Non-adherent ➔
- Treat cellular rejection and put back on immunosuppression
- ?primary problem is persistent ABMR leading to graft loss (evidence from histology)
Goals of the Workshop

2) Discuss the new developments in transplantation and their impact on patient management such as pretransplant sensitization not manifested by DSA, donor/recipient HLA epitope matching, routine posttransplant DSA monitoring

Sensitization not manifested by DSA—Hypothesis vs Memory?

Post-Transplant DSA monitoring—would be more important if there was effective therapy
Goals of the Workshop

3) Discuss the natural course of the acute-chronic AMR continuum and its temporal association with cellular rejection and changes in GFR

This is a major source of confusion. Current terminology is poor.
Antibody Mediated Rejection
Transplant Glomerulopathy: Subclinical Incidence and Association with Alloantibody

Minireview

The Spectrum of Antibody-Mediated Renal Allograft Injury: Implications for Treatment

J. Gloor, a, * F. Cosio, a D. J. Lagerb and M. D. Stegallc

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bDivision of Anatomic Pathology, Department of Laboratory Medicine and Pathology
cDivision of Transplant Surgery Department of Surgery, Mayo Clinic and Foundation, Rochester, MN
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All Prior to DSA testing with Solid Phase/LabScreen
Microvascular inflammation

Acute, active antibody mediated rejection

Peritubular capillaritis (left A) and glomerulitis (right B) are hallmark histologic features of antibody mediated rejection.
Chronic ABMR = cg
chronic transplant glomerulopathy
Meeting Report


Table 2: Revised (Banff 2013) classification of antibody-mediated rejection (ABMR) in renal allografts

**Acute/active ABMR; all three features must be present for diagnosis**¹,²

1. Histologic evidence of acute tissue injury, including one or more of the following:
   - Microvascular inflammation (g > 0² and/or ptc > 0)
   - Intimal or transmural arteritis (v > 0)⁴
   - Acute thrombotic microangiopathy, in the absence of any other cause
   - Acute tubular injury, in the absence of any other apparent cause

2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
   - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
   - At least moderate microvascular inflammation (i\(g + ptc \geq 2\)²⁴
   - Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated⁶

3. Serologic evidence of donor-specific antibodies (DSAs) (HLA or other antigens)

**Chronic, active ABMR; all three features must be present for diagnosis**¹,⁷

1. Morphologic evidence of chronic tissue injury, including one or more of the following:
   - **Transplant glomerulopathy (TG) (cp > 0)⁸** if no evidence of chronic thrombotic microangiopathy
   - Severe peritubular capillary basement membrane multilayering (requires EM)⁹
   - Arterial intimal fibrosis of new onset, excluding other causes¹⁰

2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
   - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
   - At least moderate microvascular inflammation (i\(g + ptc \geq 2\)²⁴
   - Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated⁶

3. Serologic evidence of DSAs (HLA or other antigens)
Paradigm

DSA → Microvascular inflammation (peritubular capillaritis/glomerulitis) i.e. ABMR—clinical or subclinical

Chronic ABMR → Declining GFR Graft loss
Different Clinical Scenarios

**Early Acute ABMR**
- Presensitized Patients
- High levels of DSA
- Reversible with treatment of DSA (Plex, IVIG)
- Plasmablasts/Preexisting DSA
- "Pure" ABMR on biopsy

**Late Active ABMR**
- De novo DSA and Presensitized Patients
- Variable levels of DSA
- No effective treatment
- Histology commonly mixed ACR ABMR
- Non-adherence 50%, others 50%

Creatinine

- Rare=Hard to study
- 10% by 5 years
Different Clinical Scenarios

Early Acute ABMR
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10% by 5 years
Banff 2013 criteria: ABMR

• 1) Histologic evidence of acute tissue injury resulting from ABMR and includes glomerulitis (Banff g score >0) and/or peritubular capillaritis (Banff ptc score >0), intimal or transmural arteritis (Banff v score>0), thrombotic microangiopathy, or acute tubular injury, in the absence of any other apparent cause

• 2) Evidence of current/recent antibody interaction with vascular endothelium including at least one of the following (Banff C4d score ≥2 with immunofluorescence on frozen section or Banff g+ptc score ≥2), and

• 3) Serologic evidence of donor-specific antibodies.

Banff 2013 criteria

1) Histologic evidence of acute tissue injury resulting from ABMR and includes glomerulitis (Banff g score >0) and/or peritubular capillaritis (Banff ptc score >0), intimal or transmural arteritis (Banff v score>0), thrombotic microangiopathy, or acute tubular injury, in the absence of any other apparent cause.

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Very Important in Prognosis
Banff 2013 criteria

1) Histologic evidence of acute tissue injury resulting from ABMR and includes glomerulitis (Banff g score >0) and/or peritubular capillaritis (Banff ptc score >0), intimal or transmural arteritis (Banff v score >0), thrombotic microangiopathy, or acute tubular injury, in the absence of any other apparent cause.

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3) Serologic evidence of donor-specific antibodies.


Possibly not relevant to outcome

Misses Many Grafts that Progress
Banff 2013 criteria

1) Histologic evidence of acute tissue injury resulting from ABMR and includes glomerulitis (Banff g score >0) and/or peritubular capillaritis (Banff ptc score >0), intimal or transmural arteritis (Banff v score>0), thrombotic microangiopathy, or acute tubular injury, in the absence of any other apparent cause.

2) Evidence of current/recent antibody interaction with vascular endothelium including at least one of the following (Banff C4d score ≥2 with immunofluorescence on frozen section or Banff g+ptc score ≥2), and

3) Serologic evidence of donor-specific antibodies.

Nothing is perfect

• Microvascular inflammation has the highest correlation with graft loss/50% decline in eGFR in the following 2-5 years

• DSA has a lower correlation—i.e. not all people with DSA have inflammation

• Non-HLA antibody—is this just a case where the DSA is no longer detectable in the serum?
Other Biopsy Issues: C4d and ACR

• C4d+ has a higher correlation but it may be negative in patients that progress

• All DSA is the product of a T cell dependent immune response, but we may not detect ACR on biopsy

• T cells home to sites of inflammation in ABMR

• Borderline ACR has a generally good prognosis compared to ABMR
The Utility of Protocol Biopsies in the Follow-up of Acute AMR and in the Detection of Chronic AMR
Does Early Acute $\Rightarrow$ Late Chronic?

**Early Acute ABMR**
- Presensitized Patients
- High levels of DSA
- Reversible with treatment of DSA (Plex, IVIG)
- Plasmablasts/Preexisting DSA
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**Late Active ABMR**
- De novo DSA and Presensitized Patients
- Variable levels of DSA
- No effective treatment
- Histology commonly mixed ACR ABMR
- Non-adherence 50%, others 50%

Rare=Hard to study

10% by 5 years
Preventing Early Acute ABMR does not prevent chronic ABMR

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,*

Introduction

Renal transplant candidates with high levels of antibody against a broad spectrum of HLA are very difficult to transplant. Despite receiving high priority for deceased
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Eculizumab group n = 30</th>
<th>Control group n = 48</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age at transplant (years)</td>
<td>47.8 (±1.2.7)</td>
<td>47.9 (±11.0)</td>
<td>p = 0.91</td>
</tr>
<tr>
<td>Female (%)</td>
<td>71.0%</td>
<td>78.0%</td>
<td>p = 0.36</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td>p = 0.24</td>
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<tr>
<td>Caucasian</td>
<td>96.8%</td>
<td>91.1%</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>0%</td>
<td>6.7%</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>0%</td>
<td>2.2%</td>
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<tr>
<td>Asian</td>
<td>3.2%</td>
<td>0%</td>
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<tr>
<td>Cause of renal failure (%)</td>
<td></td>
<td></td>
<td>p = 0.14</td>
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<tr>
<td>Glomerulonephritis</td>
<td>29.0%</td>
<td>33.3%</td>
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<tr>
<td>Other</td>
<td>25.8%</td>
<td>24.4%</td>
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<tr>
<td>Cystic kidney disease</td>
<td>12.9%</td>
<td>13.3%</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>9.7%</td>
<td>15.6%</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>9.7%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Congenital</td>
<td>6.5%</td>
<td>8.9%</td>
<td></td>
</tr>
<tr>
<td>Urological</td>
<td>6.5%</td>
<td>4.4%</td>
<td></td>
</tr>
<tr>
<td>Baseline B flow crossmatch mean ± SD</td>
<td>305.5±91.8</td>
<td>322.9±78.5</td>
<td>p = 0.35</td>
</tr>
<tr>
<td>HLA mismatch mean ± SD</td>
<td>3.9±1.3</td>
<td>3.3±1.4</td>
<td>p = 0.34</td>
</tr>
<tr>
<td>Retransplant (%)</td>
<td>54.8%</td>
<td>42.0%</td>
<td>p = 0.52</td>
</tr>
<tr>
<td>Class I DSA</td>
<td>36.7%</td>
<td>38.6%</td>
<td>p = 0.89</td>
</tr>
<tr>
<td>Class II DSA</td>
<td>30.0%</td>
<td>25.0%</td>
<td></td>
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<tr>
<td>Class I+II DSA</td>
<td>33.3%</td>
<td>36.4%</td>
<td></td>
</tr>
<tr>
<td>Class I DSA MFI2 mean ± SD</td>
<td>4193.3±4889.0</td>
<td>4556.68±5083.0</td>
<td>p = 0.76</td>
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<tr>
<td>Class 2 DSA MFI mean ± SD</td>
<td>4037.07±5183.3</td>
<td>3128±4141.2</td>
<td>P = 0.40</td>
</tr>
<tr>
<td>Total DSA MFI mean ± SD</td>
<td>11905.0±8985.32</td>
<td>9592.51±7808.15</td>
<td>p = 0.24</td>
</tr>
<tr>
<td>Number of pretransplant plasmapheresis mean ± SD</td>
<td>4.6±1.3</td>
<td>4.4±1.4</td>
<td>p = 0.78</td>
</tr>
<tr>
<td>Length of follow-up (months) mean ± SD (range)</td>
<td>38.2±10.2 (24.1–59.8)</td>
<td>73.0±2.50 (41.3–105.0)</td>
<td>p = 0.01</td>
</tr>
</tbody>
</table>

1 Race or ethnic group was self-reported.
Anti-C5 Treatment Protocol

Weeks
0 1 2 3 4 5 6 7 8 9 11 13

Doses (mg)
600 600 600 600 1,200 1,200 1,200 1,200 every 2 weeks

BFXM <200, stop

BFXM <200, stop
Biopsy Proven Acute Clinical ABMR

- Increase in serum creatinine >0.3mg/dl from nadir
- Biopsy showing ABMR
- First 3 months
- 43.8% controls vs 6.7% Eculizumab
- Eculizumab given for a minimum of 1 month and continued when BFXM >200 for up to 1 year
Moderate-to-Severe Peritubular capillaritis in Controls vs. Eculizumab

<table>
<thead>
<tr>
<th></th>
<th>3-4 months</th>
<th>1 year</th>
<th>2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All EC</strong></td>
<td>25.0% (7/28)</td>
<td>60.0% (18/30)</td>
<td>45.4% (10/22)</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>34.1% (14/41)</td>
<td>60.0% (21/35)</td>
<td>60.0% (15/25)</td>
</tr>
<tr>
<td><strong>p-value (control vs. EC)</strong></td>
<td>P=0.59</td>
<td>P=1.00</td>
<td>P=0.39</td>
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### Transplant Glomerulopathy in Controls vs. Eculizumab

<table>
<thead>
<tr>
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<th>3-4 months</th>
<th>1 year</th>
<th>2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All EC</strong></td>
<td>0% (0/28)</td>
<td>26.7% (8/30)</td>
<td>45.4% (10/22)</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>9.3% (4/43)</td>
<td>39.5% (15/38)</td>
<td>63.6% (21/33)</td>
</tr>
<tr>
<td><strong>p-value (EC vs. control)</strong></td>
<td>P=0.15</td>
<td>P=0.31</td>
<td>P=0.27</td>
</tr>
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</table>
### C4d in Controls vs. Eculizumab

<table>
<thead>
<tr>
<th></th>
<th>3-4 months</th>
<th>1 year</th>
<th>2 years</th>
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</thead>
<tbody>
<tr>
<td>All EC</td>
<td>46.4%</td>
<td>33.3%</td>
<td>31.8%</td>
</tr>
<tr>
<td></td>
<td>(13/28)</td>
<td>(10/30)</td>
<td>(7/22)</td>
</tr>
<tr>
<td>Control</td>
<td>17.9%</td>
<td>13.5%</td>
<td>20.7%</td>
</tr>
<tr>
<td></td>
<td>(7/39)</td>
<td>(5/37)</td>
<td>(6/29)</td>
</tr>
<tr>
<td>p-value (EC vs. control)</td>
<td>P= 0.02</td>
<td>P=0.08</td>
<td>P=0.52</td>
</tr>
</tbody>
</table>
Early C5 Blockade Prevents Late Transplant Glomerulopathy?
Lessons Learned from Eculizumab Experience

• Preventing early clinical ABMR does not prevent chronic ABMR

• Complement blockade may prevent injury in patients with low levels of DSA, but high levels of DSA are not as complement dependent

• Protocol biopsies help to delineate progression of chronic injury
Goals of the Workshop

3) Discuss the natural course of the acute-chronic AMR continuum and its temporal association with cellular rejection and changes in GFR

**Emerging Paradigm:**

Late after transplantation

Many patients present with a combination of ACR and ABMR on biopsy

ACR is the primary cause of acute rise in creatinine

ABMR is the primary cause of late graft loss in this setting (ptcitis → cg → graft loss)
Mechanism of DSA Development

• T cell dependent immune response

• Non-adherence (commonly combined with T cell mediated rejection) → may persist after treatment/resolution of the cellular response

• Planned reduction in immunosuppression—Polyoma virus, cancer or minimization/tolerance protocols

• Subclinically in otherwise adherent patients (?)50% in our series)

• Treating the ACR does not prevent late graft loss from ABMR
What you are left with

• Patient with DSA and the other problems are taken care of

• Now we can go to work
Paradigm

DSA → Microvascular inflammation (peritubular capillaritis/glomerulitis) i.e. ABMR—clinical or subclinical

Chronic ABMR → Declining GFR

Graft loss
De Novo DSA
The incidence varies with the patient population studied and how strictly it is defined.

5 years after kidney transplantation, cumulative incidence ranged from 13% (14) to 22% (15).

De Novo DSA—two studies


Not all patients with DSA lose their grafts

• Graft loss is more common when secondary to non-adherence

• Weibe AJT 2012

• Raises the question of the actual cause of graft loss in some patients

• DSA+ patients who do not develop ABMR on biopsy do well
Histologic features of Antibody Mediated Rejection. Peritubular capillaritis (left A) and glomerulitis (right B) are hallmark histologic features of antibody mediated rejection.
Paradigm

- 50% of patients with DSA develop ABMR
- More common with higher levels/C1q+
- More common with anti-Class II DSA (Dq)
- DSA+/ABMR- patients do well

Microvascular inflammation (peritubular capillaritis/glomerulitis) i.e. ABMR—clinical or subclinical
The Value of Protocol Biopsies to Identify Patients With De Novo Donor-Specific Antibody at High Risk for Allograft Loss

C. A. Schinstock¹*, F. Cosio¹, W. Cheungpasitporn⁴, D. M. Dadhania², M. J. Everly³, M. D. Samaniego-Picota⁴, L. Cornell⁵ and M. D. Stegall¹

eGFR, estimated GFR; ESRD, end-stage renal disease; IQR, interquartile range; IVIG, intravenous immunoglobulin; MFI, mean fluorescence intensity; NA, not assessed; OR, odds ratio; SAB, single antigen bead; SD, standard deviation
De Novo DSA

Consecutive Adult Solitary Kidney Transplants

N = 967

Excluded (n=196)
8 - no SAB testing pre-transplant
25 - no SAB post-transplant
5 - retransplanted during study period
158 - DSA present at time of transplant

Study Patients
(n=771)

Yearly DSA testing
Surveillance biopsies
1, 2, 5 years and when DSA detected
Mean Follow-Up
4.2 ± 1.9 years

dn DSA
N = 54

No dn DSA
N = 717
Time to de novo DSA detection

Is dnDSA lower in Tacrolimus-treated patients than in cyclosporine-treated patients? Unknown
Death-Censored Allograft Survival

The graph illustrates the survival rates of allografts over time, with different lines representing different conditions. The y-axis represents the percentage of death-censored allograft survival, while the x-axis represents the years post-transplant. The graph shows a significant difference in survival rates between groups, indicated by the p-value of less than 0.01.
Surveillance Biopsies
1 year after dnDSA detection

• 53% had acute, active ABMR (normal Creatinine)
• 37% had cABMR (cg>0)
Importantly for study design:
Prevention—treat all, graft loss rates are lower
Intervention—Enriched population, graft loss rates are higher
Easier to show an effect

Mean f/u after DN DSA Detection 3.5+2.0 years
Treatment of ABMR

• None proven effective
• Optimize tacrolimus, mmf
• Only use IVIG or plasma exchange in acute graft dysfunction
Late Antibody-Mediated Rejection in Renal Allografts: Outcome After Conventional and Novel Therapies


High Dose Intravenous Immunoglobulin Therapy for Donor-Specific Antibodies in Kidney Transplant Recipients With Acute and Chronic Graft Dysfunction

James E. Cooper, Jane Gralla, Patrick Klem, Laurence Chan, and Alexander C. Wiseman

Bortezomib Provides Effective Therapy for Antibody- and Cell-Mediated Acute Rejection

Goals of the Workshop

4) Discuss unmet medical needs and potential clinical trial design challenges for the prevention and treatment of AMR
Is there hope?

• What would a clinical trial look like?
The Problem is “Thorny”
Who to include in the study?

• ? 50% caused by non-adherence (Dr. Nickerson will cover this)
• Some secondary to necessary immunosuppressive withdrawal (polyoma virus, cancer
• Mixed cellular and humoral rejection is common
• ? Treated cellular rejection → persistent ABMR
• A conservative estimate that we used in power calculations for our proposed study is a rate of DSA detection in the overall transplant population of 2%/year after transplantation.

• This correlates to a 10% incidence at 5 years.
Combined Clinical Endpoints

• Graft loss
• 50% decline in eGFR
Surrogate endpoints

• The histologic changes of cABMR are a good surrogate biomarker for allograft loss because they precede allograft loss by years, are not seen in other conditions that affect the allograft, and are highly predictive of the outcome.

• Alternatively, just use DSA alone

• Prevention of graft loss or decline in eGFR is the ultimate goal
Chronic Irreversible Changes need to be considered in treatment

- CG3
- Ci3
- If a biopsy has a lot of chronic changes, we are less likely to treat
- Retransplantation is a better option
DSA as the inclusion criteria: Weibe et al

- 40% lost their graft by 5 years post-dnDSA.
- RCT expected to improve 5 year graft survival by 25% would require 150 recipients (power =80%, drop out 10%, p≤0.05)
- Declining GFR as an endpoint also suggested

What about a surrogate endpoint study? Shorten time to show efficacy

Surrogate=resolution of DSA
or
Surrogate=resolution of cAMR on biopsy
Design #1
DSA as the inclusion criteria
Intervention Trial

• MFI >1000
• 6 months treatment and recheck DSA
• Treat $\rightarrow$ MFI <1000
• Incidence of graft loss with MFI 1000 at 2 years is 18\% C1q might be better, but not FDA approved

Wiebe et al. Am J Transplant 2016;
Two big problems:

**DSA can resolve without treatment**

**Rate of graft loss is low**

<table>
<thead>
<tr>
<th></th>
<th>DSA Decrease</th>
<th>80%</th>
<th>90%</th>
<th>Clinical Endpoint</th>
<th>80%</th>
<th>90%</th>
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<tbody>
<tr>
<td>CTL</td>
<td>20%</td>
<td>43</td>
<td>58</td>
<td>18%</td>
<td>230</td>
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<td>Rx</td>
<td>50%</td>
<td>43</td>
<td>58</td>
<td>9%</td>
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<td>308</td>
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<tr>
<td>Total</td>
<td></td>
<td>84</td>
<td>116</td>
<td></td>
<td>460</td>
<td>608</td>
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</tbody>
</table>
Intervention Trial Design #2

• Identify patients with de novo DSA
• Biopsy
• If ABMR $\rightarrow$ Enter into trial
• If no ABMR $\rightarrow$ follow and rebiopsy
cABMR Study: Power Calculations

- cABMR does not spontaneously resolve
- 35.7% lose grafts at 2 years

<table>
<thead>
<tr>
<th></th>
<th>Histologic Response</th>
<th>80%</th>
<th>90%</th>
<th>Clinical Endpoint</th>
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<th>90%</th>
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<td>22</td>
<td>28</td>
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<td>192</td>
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</tbody>
</table>
Adaptive Trial Design

- A methodology in which a clinical trial evolves or adapts as the trial proceeds depending on the outcomes of patients enrolled.

- The criteria for these decisions are set prior to the beginning of the studies.

- An adaptive design may use of standard statistical methods (i.e. frequentist) to halt the trial early for toxicity (dangerous substance), futility (no improvement over a control), or efficacy (great improvement over a control).
Adaptive Trial Design

• can “learn” from relatively small numbers of study subjects.

• In our calculations, as few as 8 patients can be used to decide if a therapy is ineffective.

• Another aspect of ATD that enhances efficiency is that it uses a single ongoing control group rather than having a different control group for each experimental group.

• The vast majority of patients can be assigned to an experimental group. This maximizes the number of different studies that can be performed in a small population of patients.
Adaptive Trial Design

- Minimizes the number of patients receiving ineffective treatments and thus limits unnecessary treatment risks in study patients. FDA like it

- Cheaper—drug companies like it
### cABMR Study: Power Calculations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Histologic Response</th>
<th>Sample Size</th>
<th>Clinical Endpoint</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>80%</td>
<td>90%</td>
<td>80%</td>
</tr>
<tr>
<td>Control</td>
<td>0%</td>
<td>11</td>
<td>14</td>
<td>35.7%</td>
</tr>
<tr>
<td>Drug A</td>
<td>50%</td>
<td>11</td>
<td>14</td>
<td>17.9%</td>
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<tr>
<td>Total</td>
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<tr>
<td>Therapy</td>
<td>Single Therapy</td>
<td>Dual Therapy</td>
<td></td>
<td></td>
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<td>---------</td>
<td>----------------</td>
<td>--------------</td>
<td></td>
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<tr>
<td></td>
<td>[No Dual therapy]</td>
<td>[ALL Single therapy fail]</td>
<td></td>
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<tr>
<td></td>
<td>ALL</td>
<td>1 Works</td>
<td>2 Works</td>
<td>3 Works</td>
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<tr>
<td>Control</td>
<td>8</td>
<td>17</td>
<td>17</td>
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<tr>
<td>Treatment 1</td>
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</tr>
<tr>
<td>Treatment 2</td>
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<td>Treatment 3</td>
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<td>17</td>
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<tr>
<td>Treatment 1+2</td>
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<tr>
<td>Treatment 1+3</td>
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<tr>
<td>Treatment 2+3</td>
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<td>8</td>
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</tr>
</tbody>
</table>

Need 7/14 to respond
Summary
Different Clinical Scenarios

**Early Acute ABMR**
- Presensitized Patients
- High levels of DSA
- Reversible with treatment of DSA (Plex, IVIG)
- Plasmablasts/Preexisting DSA
- “Pure” ABMR on biopsy

**Late Active ABMR**
- De novo DSA and Presensitized Patients
- Variable levels of DSA
- No effective treatment
- Histology commonly mixed ACR ABMR
- Non-adherence 50%, others 50%

10% by 5 years

Rare = Hard to study

Tx 14 d 2 years
Paradigm

- DSA
  - Microvascular inflammation (peritubular capillaritis/glomerulitis)
    i.e. ABMR—clinical or subclinical

- Chronic ABMR

- Declining GFR
  - Graft loss
Biopsy

• A picture of the past and of the future

• A biomarker—how well does a biopsy finding correlate with subsequent clinical outcomes (graft loss)?
Most Important

- If your biopsy is normal, your chance of graft loss is low
Conclusions

• Developing therapy for cABMR is a major unmet need in kidney transplantation

• Validated surrogate markers are needed (histology is a very good one)

• Clinical trials are feasible

• Best to employ adaptive trial design
Reality

• Improving long-term renal allograft survival is a tough problem
• It will take many years to make improvements
• We need to start now
• I may not see the final product
Subpart H: Accelerated Approval

• Shortens time to approval
• Encourages companies to study long-term outcomes
• Drug gets FDA interim approval because it improves a predictive biomarker
• Drug can then be marked and sold
• Follow-up studies needed to show that it actually improves the clinical endpoint (ex. graft survival)
• May be “pulled” if it does not meet the clinical endpoint