Potential Primary Endpoints in Clinical Trials of Antibody-Mediated Rejection

FDA WORKSHOP on ANTIBODY MEDIATED REJECTION IN KIDNEY TRANSPLANTATION

April 12-13, 2017

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  – Canadian Institutes of Health Research

• No other relevant disclosures
The New England Journal of Medicine

1-year Graft Survival
80.4% vs 64.0% (P=0.005)

Figure 1. Product-Limit Estimates for Graft Survival in Cyclosporine-Treated Patients (Upper Curve) and Patients Given Standard Therapy (Lower Curve).
Types of Outcome Measures

- **Clinical Endpoint (Patient-important outcome)**
  - Characteristic that reflects how a patient feels, functions or how long they survive
    - *Graft survival, patient survival, quality of life*

- **Biomarker**
  - Characteristic that is objectively measured as an indicator of normal biologic processes, pathogenic processes or response to therapy
    - *Serum creatinine, GFR, proteinuria, BP etc*

- **Surrogate End-Point**
  - Biomarker that is used as a substitute for a clinical endpoint.
    - *A true surrogate is expected to predict benefit/harm.*
Surrogate End-Points

Advantages:

✓ Usually measured earlier in a trial compared to clinical endpoints
  ✷ Allows for shorter, cheaper trials to be conducted
  ✷ Results in faster decision-making about treatments - (Phase I/II)

✓ Typically surrogates are continuous variables so all patients in the trial will have an “event”
  ✷ Greatly reduces sample size, increases power and reduces cost
Disadvantages:

- Most biomarkers are NOT valid surrogate endpoints

- Surrogates are difficult to actually validate
  - Must be prognostic for a hard, clinical endpoint
  - Changes in the surrogate endpoint with treatment must predict changes in the occurrence of clinical endpoints
  - Full effect of the treatment on a clinical endpoint should be captured by the surrogate

Invalid Surrogates may Misrepresent the True Consequences of an Intervention
### Table 1. Examples of putative surrogate endpoint failures

<table>
<thead>
<tr>
<th>Disease</th>
<th>Treatment</th>
<th>Effects on</th>
<th>Trials or analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmyocardial infarction</td>
<td>Anti-arrhythmic agents</td>
<td>Reduced ventricular arrhythmia</td>
<td>CAST</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Quinidine</td>
<td>Maintained sinus rhythm at 1 year</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Milrinone/Flosequinar/ Epoprostenol</td>
<td>Improved cardiac output/increased exercise tolerance</td>
<td>PROMISE, PROFILE</td>
</tr>
<tr>
<td>Heart disease in postmenopausal women</td>
<td>Hormone replacement therapy</td>
<td>Favorable effect on serum lipoprotein level</td>
<td>FIRST, HERS</td>
</tr>
<tr>
<td>Heart disease</td>
<td>Cholesterol-lowering agents</td>
<td>Lowering cholesterol level</td>
<td>WHIT, PEP, WHO</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Sodium fluoride</td>
<td>Increased bone mineral density</td>
<td>Gordon meta-analysis</td>
</tr>
<tr>
<td>HIV</td>
<td>Zidovudine</td>
<td>Lowering CD4+ cell counts</td>
<td>British-French Concord Trial</td>
</tr>
<tr>
<td>Normotensive patients</td>
<td>Management of glaucoma</td>
<td>Lowering intraocular pressure</td>
<td></td>
</tr>
</tbody>
</table>
What Clinical Endpoints are Important to Transplant Patients?

- **Patient Survival**
- **Allograft Survival**
  - Accounts for both Patient Death and Graft Failure
  - Marker of Quality of Life
    - “Time off dialysis” while allograft functioning
  - Marker of Cost
    - Functioning transplant less costly than dialysis
  - 1-year allograft survival has been most commonly used
    - Difficult to use as an endpoint given improvements in early graft survival over time
    - To demonstrate further improvements will require sample sizes that are not feasible
Kidney Transplantation Outcomes

- **Overall** (deceased + living donor combined)
  - 1-year graft survival 94% (SRTR Website)

- **ABMR**
  - Most graft failures occur later
  - 1-year graft survival ~90%
### Sample Size Estimates for an ABMR Trial

#### Superiority Trial

<table>
<thead>
<tr>
<th>Current 1-yr Graft Survival</th>
<th>Sample Size Required to Show an Improvement in 1-yr Graft Survival to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>90%</td>
<td>92% 94% 96% 98%</td>
</tr>
<tr>
<td></td>
<td>6,426 1,442 566 276</td>
</tr>
</tbody>
</table>

**RITUX ERAH Study**

- n = 38 patients
- (21 Transplant Centers)
- (target sample size = 64)
What about Late Allograft Survival as an Endpoint? Outcomes not Clear

ABMR Outcomes
• Depends on timing of when it occurs: Early vs. Late
• Depends on treatments given
• Due to non-adherence or not
### Superiority Trial

#### Sample Size Estimates for an ABMR Trial

<table>
<thead>
<tr>
<th>Current 5-yr Graft Survival</th>
<th>Sample Size Required to Show an Improvement in 5-yr Graft Survival to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>↑2%</td>
</tr>
<tr>
<td></td>
<td>51%</td>
</tr>
<tr>
<td>78,480</td>
<td>3,130</td>
</tr>
</tbody>
</table>

**RITUX ERAH Study**

- **n = 38 patients**
- (21 Transplant Centers)
- (target sample size = 64)
It will be difficult for new interventions to show a reasonable treatment effect at 1-year or even 5-years using a realistic sample size
- It is unlikely that a new drug to prevent/treat ABMR will be so good that graft survival jumps from 90 to 98% at 1-year or 50 to 60% at 5-years

Most interventions will likely produce more modest, incremental improvements
- Sample sizes for these studies are just not feasible
What is the Ideal Endpoint for ABMR Trials?

- **Histology:** freedom from or resolution of ABMR or components (e.g. C4d); freedom from transplant glomerulopathy

- **Conventional Biomarker:** GFR, proteinuria

- **‘New’ Biomarker:** Prevention/Reduction of Donor Specific Antibody (DSA), complement fixing DSA (C1q binding), gene transcript (mRNA) expression

**These Endpoints are all Surrogates Outcome Measures**
Most Kidney Transplant Trials do NOT Measure Clinical Endpoints

Primary outcomes (1998-2008; N=285)

- Acute rejection: 72%
- Kidney function: 56%
- Blood level of substance: 27%
- Graft survival: 26%
- Patient survival: 21%
- Infection: 19%
- Bone density: 14%
- Death-censored graft survival: 4%
- Anemia: 3%
- Other hematologic: 3%
- Blood pressure: 3%
- Cardiovascular event: 2%
- Proteinuria: 2%
- Hyperglycemia: 2%
- Malignancy: 2%
- Quality of life: 1%
- Liver damage: 1%

Systematic Review
All RCTs 1998-2008
N=285

Primary Outcome
Clinical Endpoint: 22%
Surrogate: 78%
Candidate Endpoints for ABMR Trials

Clinical “Hard” Endpoints
- Patient survival
- Graft survival
- Quality of Life

Feasibility Issues

Surrogate Endpoints
- Kidney Function (GFR)
- Histology
- Donor Specific Antibody
- Gene Expression
- Proteinuria

Important but more relevant once we have proven treatments to choose from
Is Kidney Function a Valid Surrogate Outcome Measure?
Kidney Function Endpoints are Common in Transplant Trials

<table>
<thead>
<tr>
<th>Marker of kidney function</th>
<th>Primary End Point</th>
<th>Secondary End Point</th>
<th>Other End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR</td>
<td>21 (57)</td>
<td>48 (59)</td>
<td>15 (37)</td>
</tr>
<tr>
<td>4-variable MDRD Study</td>
<td>2</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Cockcroft-Gault</td>
<td>13</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>Nankivell</td>
<td>6</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Unknown/other</td>
<td>3</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>SCr</td>
<td>18 (49)</td>
<td>57 (70)</td>
<td>30 (73)</td>
</tr>
<tr>
<td>mGFR</td>
<td>7 (19)</td>
<td>7 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>$^{61}$Cr-EDTA</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>iohexol</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>$^{125}$I-iothalamate</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>iothalamate</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Combination of tracers</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Isotopic</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SCysC</td>
<td>1 (3)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Measured Ccr/unspecified MDRD Study</td>
<td>2 (5)</td>
<td>4 (5)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

Marker of kidney function used in 79% of RCTs

eGFR used in 61% of RCTs as primary or secondary outcome
Is Kidney Function a Valid Surrogate Outcome?

Is Reduced Kidney Function Associated with Worsening Graft Survival?
Post-transplant renal function in the first year predicts long-term kidney transplant survival

Sundaram Hariharan, Maureen A. McBride, Wida S. Cherikh, Christine B. Tolleris, Barbara A. Bresnahan, and Christopher P. Johnson

Authors Conclusion: “….the quality of renal function (creatinine ≤ 1.5 mg/dL at 1 year) should be implemented as a newer endpoint for primary comparative trials”
Is Kidney Function a Valid Surrogate Outcome?

Rationale for Kidney Function as a Surrogate Endpoint:

Improve Early Renal Function and you will Improve Long-term Graft Survival

Is this Rationale True in RCTs?
**Symphony Trial: Tacrolimus-Based Regimen Improved GFR**

**Table 2. Primary End Point and Selected Secondary End Points.**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Standard-Dose Cyclosporine (N=390)</th>
<th>Low-Dose Cyclosporine (N=399)</th>
<th>Low-Dose Tacrolimus (N=401)</th>
<th>Low-Dose Sirolimus (N=399)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean calculated GFR — ml/min‡</td>
<td>57.1±25.1</td>
<td>59.4±25.1</td>
<td>65.4±27.0</td>
<td>56.7±26.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value for comparison with tacrolimus</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>Reference</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Tacrolimus-Based Regimen Also Associated with Better Allograft Survival

<table>
<thead>
<tr>
<th>Allograft survival</th>
<th></th>
<th>Standard-Dose Cyclosporine (N = 390)</th>
<th>Low-Dose Cyclosporine (N = 399)</th>
<th>Low-Dose Tacrolimus (N = 401)</th>
<th>Low-Dose Sirolimus (N = 399)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Censored for death of patients with functioning allograft — %</td>
<td>91.9</td>
<td>94.3</td>
<td>96.4</td>
<td>91.7</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>P value for comparison with tacrolimus</td>
<td>0.007</td>
<td>0.18</td>
<td>Reference</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncensored for death of patients with functioning allograft — %</td>
<td>89.3</td>
<td>93.1</td>
<td>94.2</td>
<td>89.3</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>P value for comparison with tacrolimus</td>
<td>0.01</td>
<td>0.56</td>
<td>Reference</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Is Kidney Function a Valid Surrogate Outcome?

- Is the full effect of treatment on clinical endpoint (graft survival) captured by the surrogate (GFR)?
  
  • Not entirely clear

  • Tacrolimus also significantly reduced acute rejection – maybe this was the pathway to improved graft outcome??

Is GFR a Valid Surrogate Outcome?

Low Dose Tacrolimus + MMF

Alternate Pathway for Treatment to Work

Reduced Acute Rejection

“Better Immunosuppression”

Increased Graft Survival

“Less Toxicity was Hypothesized”

Kidney Tx

↑GFR
Comparison of the Predictive Performance of eGFR Formulae for Mortality and Graft Failure in Renal Transplant Recipients

**eGFR is Strongly Associated with Mortality and Graft Loss**

<table>
<thead>
<tr>
<th>Formula studied</th>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft-Gault</td>
<td>eGFR</td>
<td>0.96</td>
<td>0.95–0.98</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Walser</td>
<td>eGFR</td>
<td>0.96</td>
<td>0.95–0.98</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Nankivell</td>
<td>eGFR</td>
<td>0.97</td>
<td>0.95–0.98</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>MDRD 7</td>
<td>eGFR</td>
<td>0.97</td>
<td>0.96–0.98</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>aMDRD</td>
<td>eGFR</td>
<td>0.97</td>
<td>0.96–0.99</td>
<td>$0.0004$</td>
</tr>
<tr>
<td>RR-MDRD</td>
<td>eGFR</td>
<td>0.97</td>
<td>0.96–0.98</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>eGFR</td>
<td>0.97</td>
<td>0.96–0.98</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>

*Transplantation 2009;87: 384–392*
n=1,344 patients

Predictor: 6-month eGFR

Prediction of 5-year graft survival even worse

<table>
<thead>
<tr>
<th>Predictor</th>
<th>c-statistic</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft-Gault</td>
<td>0.597</td>
<td>0.486, 0.709</td>
</tr>
<tr>
<td>MDRD 7</td>
<td>0.626</td>
<td>0.504, 0.748</td>
</tr>
<tr>
<td>Rule’s Refitted MDRD</td>
<td>0.628</td>
<td>0.508, 0.748</td>
</tr>
<tr>
<td>Abbreviated MDRD</td>
<td>0.639</td>
<td>0.521, 0.756</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>0.642</td>
<td>0.525, 0.758</td>
</tr>
<tr>
<td>Nankivell</td>
<td>0.650</td>
<td>0.542, 0.758</td>
</tr>
<tr>
<td>Walser</td>
<td>0.657</td>
<td>0.544, 0.770</td>
</tr>
</tbody>
</table>

Transplantation 2009;87: 384–392
49% of graft failure in this series occurred in patients thought to have an excellent prognosis – i.e. Those with GFR > 40 at 1-year
Patients with Good GFR at 1-year who Progressed (High-P) had More Grant Loss than the Low GFR Group

Although not Intuitive, Early Renal Function tells us Little about the Risk of Late Graft Failure in Many Patients
Why is the GFR at a fixed time often poorly predictive of long-term outcomes?

- eGFR/creatinine may be a poor marker of true GFR
- “True GFR” may not reflect severity of underlying disease/pathology in the allograft
- One eGFR/creatinine value may not reflect true baseline or ‘steady state’
- Lots can occur after 6 or 12 months
  - Stop taking medication
  - Recurrent disease
  - Late rejection
  - Other medical complication: e.g. infection, cancer, NODAT, MI, CHF etc
What about decline in kidney function over time

Is this more predictive?
Doubling of Cr (-57% decline in GFR) - Standard Kidney Function Endpoint

-57% decline or greater:
- 10-yr risk of ESRD 99%
- Occurred in 0.79%

-30% decline or greater:
- 10-yr risk of ESRD 64%
- Occurred in 6.9%

HR 32.1 (22.3 - 46.3)  HR 5.4 (4.5 - 6.4)

Examined lesser declines in GFR and association with ESRD
Relationship between eGFR Decline and Hard Outcomes after Kidney Transplants

Philip A. Clayton,*,†† Wai H. Lim,*,§ Germaine Wong,*†‖ and Steven J. Chadban*†

**B** Overall graft failure

- **C** Death-censored graft failure

HR 3.58 (3.16 - 4.05)

HR 5.14 (4.44 - 5.95)

**Relationship between eGFR Decline and Hard Outcomes after Kidney Transplants**

Philip A. Clayton,*†‡ Wai H. Lim,*§ Germaine Wong,*†|| and Steven J. Chadban*†‡

<table>
<thead>
<tr>
<th>eGFR Decline</th>
<th>Prevalence, %</th>
<th>Graft Failure</th>
<th>Patient Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>c Statistic</td>
</tr>
<tr>
<td>≥10%</td>
<td>33</td>
<td>2.09 (1.91 to 2.29)</td>
<td>0.68</td>
</tr>
<tr>
<td>≥20%</td>
<td>19</td>
<td>2.50 (2.26 to 2.77)</td>
<td>0.69</td>
</tr>
<tr>
<td>≥30%</td>
<td>10</td>
<td>3.58 (3.16 to 4.05)</td>
<td>0.70</td>
</tr>
<tr>
<td>≥40%</td>
<td>5</td>
<td>5.24 (4.43 to 6.20)</td>
<td>0.69</td>
</tr>
<tr>
<td>≥50%</td>
<td>3</td>
<td>7.90 (6.21 to 10.06)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

**Smaller Declines in GFR Occurred more Commonly**

**Similar Relationship: GFR Decline and Graft Failure; GFR Decline and Death**

**c-Statistics Similar – No Specific Cut Point was Better**

**C-Statistics Good but not Great**
Is Donor Specific Antibody (DSA) a Valid Surrogate Outcome Measure?
Reducing De Novo Donor-Specific Antibody Levels during Acute Rejection Diminishes Renal Allograft Loss


A. Immunodominant DSA Level Responder Group

B. Immunodominant DSA Level Non-Responders Group

Reducing De Novo Donor-Specific Antibody Levels during Acute Rejection Diminishes Renal Allograft Loss

M. J. Everly\textsuperscript{a,*}, J. J. Everly\textsuperscript{a}, L. J. Arend\textsuperscript{c}, P. Brailey\textsuperscript{b}, B. Susskind\textsuperscript{b}, A. Govil\textsuperscript{d}, A. Rike\textsuperscript{a}, P. Roy-Chaudhury\textsuperscript{d}, G. Mogilishetty\textsuperscript{d}, R. R. Alloway\textsuperscript{d}, A. Tevar\textsuperscript{a} and E. S. Woodle\textsuperscript{a,*}

A Banff Component Scoring-based Histologic Assessment of Bortezomib-based Antibody-mediated Rejection Therapy

Basma Sadaka,¹ Nicole S. Ejaz,² Adele R. Shields,² Michael A. Cardi,³ George Wadih,⁴ David Witte,⁵,⁶ Bassam G. Abu Jawdeh,¹ Rita R. Alloway,¹ and E. Steve Woodle²

1-year Graft Survival

>50% Reduction in DSA: 100%

≤50% Reduction in DSA: 57.1%
Are Histologic Markers Valid Surrogate Outcome Measures?
A Banff Component Scoring-based Histologic Assessment of Bortezomib-based Antibody-mediated Rejection Therapy

Basma Sadaka,¹ Nicole S. Eajaz,² Adele R. Shields,² Michael A. Cardi,³ George Wadih,⁴ David Witte,⁵,⁶ Bassam G. Abu Jawdeh,¹ Rita R. Alloway,¹ and E. Steve Woodle²

N=55 Treated with Bortezomib
Pre-Post Treatment Biopsies
A Banff Component Scoring-based Histologic Assessment of Bortezomib-based Antibody-mediated Rejection Therapy

Basma Sadaka, 1 Nicole S. Ejaz, 2 Adele R. Shields, 2 Michael A. Cardi, 3 George Wadih, 4 David Witte, 5,6 Bassam G. Abu Jawdeh, 1 Rita R. Alloway, 1 and E. Steve Woodle 2

A

Acute Scores

B

Chronic Scores

Acute Composite Score: Possible Surrogate?
Need Correlation with Late Graft Failure
Subclinical Rejection Phenotypes at 1 Year Post-Transplant and Outcome of Kidney Allografts

Alexandre Loupy,† Dewi Vernerey,† Claire Tinel,† Olivier Aubert,* Jean-Paul Duong van Huyen,* Marion Rabant,§ Jérôme Verine,‖ Dominique Nochy,‖ Jean-Philippe Empana,* Frank Martinez,‖ Denis Glotz,** Xavier Jouven,* Christophe Legendre,*† and Carmen Lefaucheux**

A

Graft survival Probability

logrank p < 0.0001

- No rejection (n=727)
- Subclinical TCMR (n=132)
- Subclinical ABMR (n=142)

Time post transplantation (years)

Independent of GFR and proteinuria

Absence of ABMR on Biopsy – Possible Surrogate Outcome Measure?
Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study

**Table 1:** Antibody-mediated rejection scorecard based on biopsy characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4d score</td>
<td>Percent of PTC that stained positive for C4d (by immunofluorescence) (0–100%).</td>
</tr>
<tr>
<td>Margination score</td>
<td>Percent area (on the allograft biopsy section) involved in PTC margination, by neutrophils and/or monocytes (0–100%).</td>
</tr>
<tr>
<td></td>
<td>Banff Classification (2,9) PTC (margination) score (0, 1, 2, or 3).</td>
</tr>
<tr>
<td>Glomerulitis score</td>
<td>Percent of glomeruli (on the allograft biopsy section) that had the appearance of active inflammation (0–100%).</td>
</tr>
<tr>
<td>Vasculitis score</td>
<td>Percent of intimal luminal reduction in diameter (0–100%) from the 1 artery (on the allograft biopsy section) considered by the pathologist to be the most damaged by arteritis (arterial inflammation).</td>
</tr>
<tr>
<td></td>
<td>Any inflammation and/or fibrinoid necrosis of the smooth muscle wall on any artery on the section? (yes/no)</td>
</tr>
<tr>
<td>Glomerulosclerosis score</td>
<td>Percent of glomeruli (on the allograft biopsy section) that had glomerulosclerosis (0–100%).</td>
</tr>
<tr>
<td>Chronic glomerulopathy score</td>
<td>Percent of the most involved glomerulus (on the allograft biopsy section) with “double contouring” of the tuft (as determined by the pathologist; 0–100%).</td>
</tr>
<tr>
<td>Interstitial fibrosis score</td>
<td>Percent of the cortex (on the allograft biopsy section) that was fibrotic (0–100%).</td>
</tr>
<tr>
<td>Chronic vasculitis score</td>
<td>Percent of arterial lumen narrowing by fibrointimal thickening was recorded (0–100%) for the most severely involved artery (on the allograft biopsy section) as determined by the pathologist.</td>
</tr>
</tbody>
</table>
Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study

<table>
<thead>
<tr>
<th>Histopathology end point</th>
<th>Placebo (n = 9)</th>
<th>C1 INH (n = 9)</th>
<th>p-value for treatment difference $^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Qualifying biopsy</td>
<td>Day-20 biopsy</td>
<td>Change</td>
</tr>
<tr>
<td>C4d score</td>
<td>60.8 ± 41.2</td>
<td>15.8 ± 32.9</td>
<td>−45.0 ± 46.9</td>
</tr>
<tr>
<td>Margination score</td>
<td>23.0 ± 24.8</td>
<td>17.0 ± 25.8</td>
<td>−6.0 ± 14.0</td>
</tr>
<tr>
<td>Glomerulitis score</td>
<td>17.0 ± 24.9</td>
<td>23.7 ± 30.9</td>
<td>6.7 ± 26.6</td>
</tr>
<tr>
<td>Vasculitis score</td>
<td>3.9 ± 7.8</td>
<td>0 ± 0.0</td>
<td>−3.9 ± 7.8</td>
</tr>
<tr>
<td>Glomerulosclerosis score</td>
<td>4.2 ± 6.8</td>
<td>2.8 ± 3.6</td>
<td>−1.4 ± 7.8</td>
</tr>
<tr>
<td>Chronic glomerulopathy score</td>
<td>0.3 ± 1.0</td>
<td>0.6 ± 1.7</td>
<td>0.2 ± 0.7</td>
</tr>
<tr>
<td>Interstitial fibrosis score</td>
<td>3.2 ± 6.6</td>
<td>9.1 ± 14.1</td>
<td>5.9 ± 9.8</td>
</tr>
<tr>
<td>Chronic vasculitis score</td>
<td>8.3 ± 12.8</td>
<td>6.7 ± 11.7</td>
<td>−1.7 ± 18.2</td>
</tr>
</tbody>
</table>

None of the biopsy components improved by Day-20

6-month biopsy on subset of n=14 patients
C1 INH: 0/7 (0%) had TG
Placebo: 3/7 (43%) had TG

No change in histology except C4d
(p=0.045)

GFR improved from 38.7±17.9 to 45.2±21.3
(p=0.027)
Primary Endpoint: ABMR in first 3-months

- Eculizumab: 7.7%
- Control: 41%
Are Gene Expression Measurements (‘Molecular Microscope’) Valid Surrogate Outcome Measures?
The classifier output is a score between 0.0 - 1.0
Reflects the probability that ABMR is operating in the biopsy

Score of 0.2 used as a threshold to define a case as positive for ABMR
AUC=0.89
Any S+ (ABMR score >0.2) associated with a bad outcome
C+ on its own associated with late but not early failure

Perhaps ABMR Score could be a possible surrogate?
Advantages:
• Combine infrequent events together to allow sufficient sample sizes

Potential Disadvantages:
• Components of the endpoint not of similar importance
  • Is persistence of DSA the same as graft loss?
• Components may not occur with similar frequency
  • Often ‘less serious’ endpoint occurs most often
• Different relative risk reductions for each component of the composite
  • Ideal situation occurs when the biology of the components is similar enough so that each has a similar RRR
Clinical Factors: ACR, Serum Albumin, eGFR, Acute Rejection, Race, Sex, Age

Histology at 1-year: Glomerulitis, Chronic Interstitial Fibrosis (g and ci scores)

DSA: (Class II DSA Level)
Predicting Individual Renal Allograft Outcomes Using Risk Models with 1-Year Surveillance Biopsy and Alloantibody Data

Risk Calculator

Accurate prediction of kidney transplant failure remains imperfect. A recent study by Bormus et al showed that data available 12 months post transplantation could usefully predict 5-year transplant failure. The calculator below can be used to accurately predict 5-year death censored renal transplant survival with variables at 1 year post transplantation. For full details on the development the calculator and the statistical models involved we would direct the reader to the published article.

UACR (mg/mmol): 36.3
Albumin (g/L): 37
eGFR (mL/min): 40
Acute rejection (any severity): no
Recipient Ethnicity: Asian
Recipient sex: Female
Recipient age (years): 45

5-year risk % death censored graft loss: 13.6
5-year risk % graft loss (including death with graft function): 14.8

Accepted input ranges are as follows
ACR: 0.1-1200 mg/mmol (please note units used)
Albumin: 10-60 g/L
eGFR: 5-120 mL/min (4-variable MDRD Study equation with IDMS-traceable creatinine)

Ethnicities other than White, South Asian, or Black cannot be accounted for in the score, and therefore ethnicity should be entered as deemed appropriate based on clinical outcomes in that group.

Model Performed Well Except Some Underestimation at Higher Risk Groups

JASN 27: 3165–3174, 2016
Predicting Individual Renal Allograft Outcomes Using Risk Models with 1-Year Surveillance Biopsy and Alloantibody Data

Manuel Moreno Gonzales,* Andrew Bentall,†‡ Walter K. Kremers,* Mark D. Stegall,* and Richard Borrows†‡

Death-Censored Graft Failure

Histology Added to the Model
Glomerulitis and Chronic Interstitial Fibrosis (g and ci scores)
c-Statistic Improved:
0.84 to 0.90

Adding DSA to the Model Did Not Improve Prediction (c=0.82)

JASN 27: 3165–3174, 2016
Molecular Microscope Strategy to Improve Risk Stratification in Early Antibody-Mediated Kidney Allograft Rejection

Table 4. Determinants of kidney transplant graft outcome after acute ABMR (multivariate models) using the ABMR Molecular Score and endothelial DSA-selective transcripts

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number of Patients</th>
<th>Number of Events</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 with ABMR Molecular Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor age, yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>54</td>
<td>11</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>≥60</td>
<td>20</td>
<td>10</td>
<td>3.84</td>
<td>1.48 to 9.96</td>
<td>0.01</td>
</tr>
<tr>
<td>eGFR* (ml/min) at the time of rejection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>52</td>
<td>10</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>&lt;30</td>
<td>22</td>
<td>11</td>
<td>1.74</td>
<td>0.70 to 4.33</td>
<td>0.23</td>
</tr>
<tr>
<td>Humoral histologic score (g+ptc+v+cg+C4d)</td>
<td>74</td>
<td>21</td>
<td>1.43</td>
<td>1.09 to 1.90</td>
<td>0.01</td>
</tr>
<tr>
<td>ABMR Molecular Score</td>
<td>74</td>
<td>21</td>
<td>2.22</td>
<td>1.37 to 3.58</td>
<td>0.001</td>
</tr>
</tbody>
</table>

ABMR Molecular Score (Independent of Histology) Associated with Graft Failure

ABMR Score Improved Model Discrimination
AUC Significantly Improved from 0.77 to 0.81
Difference = 0.049 (0.047 to 0.052)

Is Proteinuria a Valid Surrogate Outcome Measure?
### Degree of Proteinuria (Independent of Histology) Associated with Graft Failure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 2: With proteinuria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria at time of biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3–1.0 versus &lt;0.3 g/24 h</td>
<td>1.14 (0.81–1.60)</td>
<td>0.50</td>
</tr>
<tr>
<td>1.0–3.0 versus &lt;0.3 g/24 h</td>
<td>2.17 (1.49–3.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;3.0 versus &lt;0.3 g/24 h</td>
<td>3.01 (1.75–5.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR at time of biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–45 versus &gt;45 mL/min per m²</td>
<td>1.76 (0.59–5.30)</td>
<td>0.31</td>
</tr>
<tr>
<td>15–30 versus &gt;45 mL/min per m²</td>
<td>5.53 (1.99–15.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt;15 versus &gt;45 mL/min per m²</td>
<td>11.7 (4.17–33.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>g+ptc ≥2 versus &lt;2</td>
<td>1.36 (0.97–1.91)</td>
<td>0.07</td>
</tr>
<tr>
<td>Banff grade 1 versus 0</td>
<td>1.82 (1.25–2.64)</td>
<td>0.002</td>
</tr>
<tr>
<td>Banff grade 2–3 versus 0</td>
<td>3.45 (2.34–5.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Banff grade 1 versus 0</td>
<td>1.00 (0.55–1.82)</td>
<td>0.99</td>
</tr>
<tr>
<td>Banff grade 2–3 versus 0</td>
<td>1.83 (1.11–3.04)</td>
<td>0.02</td>
</tr>
<tr>
<td>De novo/recurrent glomerular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present versus absent</td>
<td>1.35 (0.84–2.19)</td>
<td>0.22</td>
</tr>
<tr>
<td>Polyomavirus associated nephropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present versus absent</td>
<td>5.51 (3.06–9.92)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
1-yr Proteinuria Predictive of Graft Failure at 5-Yrs, Even in those Patients with TG

Which Outcome Measure to Use?

• Depends on the Trial Purpose
  • Prevention vs Treatment

• Focus on Efficacy
  • Safety endpoints equally important
  • Death, overall infections, BK, CMV, PTLD/Cancer

• Suggestions for Discussion
  • NONE are Properly Validated in Trials
ABMR “Treatment” Trial - Potential Composite Endpoint

- >30% eGFR Decline (from study entry to 1-year later); or
  (Function Outcome)

- “Bad” features on 12-month Protocol Biopsy; or
  - Microvascular Inflammation (g and ptc scores)
  - C4d
  - TG (cg score)
  (Histology Outcome)

- ABMR Molecular Score >0.2 (1-yr)
  (Molecular Outcome)

- <50% Reduction in DSA; or
  (DSA Outcome)

- 24-hr Protein > 500 mg at 1-yr if TG present on Bx
  (Proteinuria/‘Damage’ Outcome)

Completely Arbitrary Selection of Outcomes and Cut-Offs

We Need to Start Measuring Similar Outcomes Pre and Post-Treatment to Determine what is Responsive and Predictive
ABMR “Prevention” Trials – Potential Endpoint

- **Clinical ABMR** in the first year using current Banff criteria; or
  (Histology + DSA Outcome)

- “Bad” features on 12-month Protocol Biopsy; or
  - Microvascular Inflammation (g and ptc scores)
  - C4d
  - TG (cg score)
  (Histology Outcome)

- ABMR Score >0.2 on Protocol Bx; or
  (Molecular Outcome)

- Development of dnDSA; or
  (DSA Outcome)

- 24-hr Protein > 500 mg at 1-yr if TG present on Bx
  (Proteinuria/‘Damage’ Outcome)
Summary

- It is difficult to use patient-important outcomes such as graft survival in ABMR trials given sample sizes required to show realistic treatment effects.

- Surrogate endpoints are commonly used in renal transplant trials – especially measures of kidney function such as GFR.

- While convenient from a sample size and power perspective, most surrogates are not well validated.
Summary

- Surrogate outcomes and composite measures involving several surrogates will be necessary for ABMR trials.

- Likely candidate outcomes for ABMR studies include GFR, histology, molecular transcripts, DSA and proteinuria as well as combinations of these endpoints.

- Validation of these endpoints needs to occur – we need to begin measuring candidate outcomes before and after ABMR treatments to see how they respond.

- Long-term follow-up will be needed for all ABMR trials using surrogates to evaluate their eventual effect on hard clinical endpoints such as graft survival.
Potential Primary Endpoints in Clinical Trials of Antibody-Mediated Rejection

FDA WORKSHOP on ANTIBODY MEDIATED REJECTION IN KIDNEY TRANSPLANTATION

April 12-13, 2017

Greg Knoll MD MSc
Professor of Medicine, University of Ottawa
Senior Scientist, Ottawa Hospital Research Institute