Eculizumab chez les receveurs de greffe rénal à haut risque immunologique

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Disclosure.

• Dr Mark Stegall.
• Institution: Mayo Clinic, Rochester.
• Research contracts with Alexion and Millenium
• My presentation includes discussion of off-label and investigational.
• Yes—Eculizumab, Alexion Pharmaceuticals; Velcade, Millenium
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• Steve DeGoey
• Manish Gandhi
• Jeff Winters
• Lynette Fix
• Kay Kosberg
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Preexisting Donor-Specific HLA Antibodies Predict Outcome in Kidney Transplantation

Carmen Lefaucheux, Alexandre Loupy, Gary S. Hill, João Andrade, Dominique Nochy, Corinne Antoine, Chantal Gautreau, Dominique Charmon, Denis Glotz, and Caroline Suberbielle-Boissel

Departments of *Nephrology and Kidney Transplantation and Immunology and Histocompatibility, Saint-Louis Hospital, Paris, France; and "Department of Histopathology", Groupe Broussais European Hospital, Paris, France

AMR % with MFI

3001-6000 = 36.4%
>6000 = 51.3%
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Alloantibody Levels and Acute Humoral Rejection Early After Positive Crossmatch Kidney Transplantation

J. M. Burns\textsuperscript{a}, L. D. Cornell\textsuperscript{b}, D. K. Perry\textsuperscript{a}, H. S. Pollinger\textsuperscript{a}, J. M. Gloor\textsuperscript{c}, W. K. Kremers\textsuperscript{d}, M. J. Gandhi\textsuperscript{b}, P. G. Dean\textsuperscript{a} and M. D. Stegall\textsuperscript{a,*}

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We examined the course of donor-specific alloantibody (DSA) levels early after transplant and their relationship with acute humoral rejection (AHR) in two groups of positive crossmatch (+XM) kidney transpheresis; SABs, single antigen beads; +XM, positive crossmatch.

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Introduction

Donor-specific alloantibody (DSA) is an increasingly common finding in renal transplant candidates (1). With the development of more sensitive assays, it is now clear that DSA levels vary widely among these patients and that the serum level of DSA may be the major determinant of allograft injury (2). For example, patients with high levels of DSA at the time of transplant appear to have a high risk for
Alloantibody Levels and Acute Humoral Rejection Early After Positive Crossmatch Kidney Transplantation

**Early AMR:**

*May cause early graft loss*

*Associated with shortened graft survival*

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May cause early graft loss
Associated with shortened graft survival
Expensive and increases morbidity

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planted injury (AMR). Examples of patients with high-to-
early DSA at the time of transplant appear to have a high risk for
Antibody Mediated Rejection: Positive Crossmatch Recipients

- "Pure" AMR, absence of features of acute cellular rejection
- Thrombotic microangiopathy
- C4d+
- Graft dysfunction (↑>0.3 mg/dl)
- Mean time to onset ~ 10 days
- Increased DSA = ? Assay
Spectrum of AMR
Low baseline DSA levels (B-FXM) without AHR

High baseline DSA levels (B-FXM) without AHR

Low baseline DSA levels (B-FXM) with AHR

High baseline DSA levels (B-FXM) with AHR

Burns et al Am J Transplant 2008; 8:2684-2694
Measuring Donor Specific Alloantibody
I. Solid phase assay
   (LABscreen/Luminex)

**Pro:** Standardized, Commercially-available beads

**Cons:**
- Multiple DSA—which to use? Highest vs adding all together
- Different HLA densities on different beads
- Not FDA approved for measuring amount

**During AMR**
- 64% had both anti-donor Class I and II
- 20% had only anti-donor Class I (10% had 2)
- 16% had only Class II only
Measuring Donor Specific Alloantibody
II. Cell-based assays
(T cell AHG, T/B flow cytometric crossmatch)

**Pro:**
- Correlation with clinical outcomes (locally)
- Ability to "sum anti-Class I + II (BFXM)—B cells express both I and II"

**Cons:**
- T cells express only Class I
- Lack of standardization
- Poor acceptance of BFXM by transplant community
- Variability from day-to-day
- None FDA approved
Figure 1: Correlation between fluorescence channels and molecules of equivalent soluble fluorescence units (MESF) in our laboratory. This standardized curve was generated retrospectively to allow comparisons between our laboratory’s flow crossmatch channel shift data to data available in other laboratories. The curve was generated via a linear regression model with
AMR and B Flow Cytometric Crossmatch

Burns et al.

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<th>B-cell FXM</th>
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<th>Sensitivity</th>
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### AMR and MFI (total)

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New Approaches to AMR
Treat ongoing AMR

Proteasome inhibition mostly with mixed antibody and cellular rejection

No controlled studies

Difficult to show efficacy over other therapies (ex. Plasma Exchange)
Bortezomib Provides Effective Therapy for Antibody- and Cell-Mediated Acute Rejection


Background. Current antihumoral therapies in transplantation and autoimmune disease do not target the mature antibody-producing plasma cell. Bortezomib is a first in class proteasomal inhibitor, that is Food and Drug Administration approved, for the treatment of plasma cell-derived tumors that is multiple myeloma. We report the first clinical experience with plasma cell-targeted therapy (bortezomib) as an antirejection strategy.

Methods. Eight episodes of mixed antibody-mediated rejection (AMR) and acute cellular rejection (ACR) in six transplant recipients were treated with bortezomib at labeled dosing. Monitoring included serial donor-specific antihuman leukocyte antigen antibody (DSA) levels and repeated allograft biopsies.

Results. Six kidney transplant patients received bortezomib for AMR and concomitant ACR. In each case, bortezomib therapy provided (1) prompt rejection reversal, (2) marked and prolonged reductions in DSA levels, (3) improved renal allograft function, and (4) suppression of recurrent rejection for at least 5 months. Moreover, immunodominant DSA (IDSA) (i.e., the antidonor human leukocyte antigen antibody with the highest levels) levels were decreased by more than 50% within 14 days and remained substantially suppressed for up to 5 months. One or more additional DSA were present at lower concentrations (non-IDSA) in each patient and were also reduced to nondetectable levels. Bortezomib-related toxicities (gastrointestinal toxicity, thrombocytopenia, and paresthesia) were all transient.

Conclusions. Bortezomib therapy: (1) provides effective treatment of AMR and ACR with minimal toxicity and (2) provides sustained reduction in IDSA and non-IDSA levels. Bortezomib represents the first effective antihumoral therapy with activity in humans that targets plasma cells.

Keywords: Proteasome Inhibitor, Bortezomib, Plasma cell, B cell, Alloantibodies.
Proteasome Inhibition Causes Apoptosis of Normal Human Plasma Cells Preventing Alloantibody Production

D. K. Perry\textsuperscript{a}, J. M. Burns\textsuperscript{a}, H. S. Pollinger\textsuperscript{b}, B. P. Amiot\textsuperscript{d}, J. M. Gloor\textsuperscript{b}, G. J. Gores\textsuperscript{c} and M. D. Stegall\textsuperscript{a, \ast}

\textsuperscript{a}Division of Transplantation Surgery, Department of Surgery, \textsuperscript{b}Division of Nephrology and Hypertension, \textsuperscript{c}Division of Gastroenterology and Hepatology, Department of Internal Medicine, von Liebig Center, Mayo Clinic College of Medicine, Rochester, \textsuperscript{d}Renal Biomedical Incorporated, Minneapolis, USA

The Impact of Proteasome Inhibition on Alloantibody-Producing Plasma Cells In Vivo

Tayyab S. Diwan, Suresh Raghavaiah, Justin M. Burns, Walter K. Kremers, James M. Gloor, and Mark D. Stegall

Background. Donor-specific alloantibody-producing plasma cells (DSA PCs) appear resistant to conventional immunosuppressive agents. This study aimed to determine the impact of proteasome inhibitor bortezomib on DSA-PCs in sensitized renal allograft candidates and to assess if DSA-PC depletion would enhance the efficacy of DSA removal using plasma exchange (PE).

Methods. Only patients with DSA levels considered too high to successfully undergo transplantation with PE alone were included in this study. Those with a baseline 3-flow cytometric crossmatch (BCXM) > 450 against a potential living donor. Four sensitized patients received 4 doses (13 mg/m\textsuperscript{2}dose) of bortezomib and 4 received 16 doses. The number of DSA-PCs was determined pre and post-treatment using an ILLISPT assay. Five of these patients underwent post-treatment PE and their response was compared to 8 highly sensitized patients (BCXM > 450) who underwent PE alone.

Results. When considering all 13 patients as a group, bortezomib treatment decreased DSA-PCs in the narrow mean (SD) = 16.2 ± 14.3 DSA-PCs/ml pre-treatment vs. 12.3 ± 11.3 DSA-PCs/ml after treatment, P=0.048. In the time frame of the study, bortezomib alone did not decrease serum DSA levels. However, five bortezomib-treated patients underwent PE and showed a greater decrease in DSA compared to the historical control group of 8 sensitized patients who underwent PE alone (mean decrease in BCXM channel shift = 27.9 ± 9.2 units with bortezomib vs. 56.4 ± 72.1 units in PE alone P=0.008).

Conclusions. Bortezomib depletes DSA-PCs and appears to potentiate DSA removal by PE in sensitized transplant recipients.

Keywords: Proteasome inhibitor, Alloantibodies, Plasma cells, Clinical kidney transplantation, Sensitized patients.
Preventing AMR
Hypothesis

• Almost all cases of AMR show evidence of complement activation—C4d+ peritubular capillaries

• Inhibition of terminal complement activation with anti-C5 antibody (eculizumab) will prevent AMR in +XM Kidney Transplantation
The Complement Cascade: Targeted Inhibition

**Classical Pathway**
Antigen/Antibody Complexes

**Activated C1**

**C3 Convertase**

**C5 Convertase**

**Potent Anaphylatoxin**
Chemotaxis
Cell Activation

**Cell Activation**
Neisseria Clearance
RBC Lysis

**Activated MBL**
C4+C2

**C3 Convertase**

**C5 Convertase**

**C5b-9**

**Eculizumab Target**

**Lectin Pathway**
Carbohydrate Structures

**Activated MBL**

**C4b2a**

**C4b2a3b**

**C5a**

**C5b**

**C6 C7 C8 C9**

**Immune Complex**
Microbial Opsonization

**Weak Anaphylatoxin**

**C3a**

**C3**

**C4b2a**

**C3 Convertase**

**C3b**

**C3bBb**

**C3bBb3b**

**C3**

**Factor B+D**

**C3H2O**
Tickover

**Alternative Pathway**
M/O and Mammalian Cell Membranes
Pretransplant Management
Same in Both Groups

Baseline T/B FXM

<300
- No PE
- Monitor DSA post-transplant

>300
- Pretransplant PE to achieve T and B FXM <300

Thymoglobulin induction, Prograf, Mycophenolate mofetil, Prednisone
Anti-C5 Treatment Protocol

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

- Dose (mg): 1,200, 600, 600, 600, 1,200, 1,200, 1,200, 1,200 every 2 weeks

- BFXM <200, stop

No post-transplant plasmapheresis.
Biopsy on days 4, 7, 14, 28, and 90.
1º Endpoint

- Incidence of AMR in first 90 days post-transplant
  - Thrombotic microangiopathy
  - Graft dysfunction (↑>0.3 mg/dl)
- Protocol biopsies at day 0, 4, 7, 10, 14, 21, 28
- Serum for SABs and T/B FXM
Study Design

BFXM 200→450
MFI 3000-12,000+

Historical Controls
N=51
• 1/1/05—10/1/07
• PE-based “desensitization”
• Consecutive Patients

Anti-C5 Treated
N=26
6/1/08—09/27/10
• Added to existing PE-based protocol

1 patient in each group had BFXM <450, but failed to reach <300 with PE
## Patients

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<th>Control Group (n=51)</th>
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<td>Age in years at time of transplantation (Mean ± SD)</td>
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<td>48.4 ± 11.4</td>
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<td>13 (25%)</td>
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</tr>
<tr>
<td><strong>Donor-Specific Alloantibody Levels</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B flow crossmatch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline channel shift (mean ± SD)</td>
<td>330 ± 84</td>
<td>327 ± 73</td>
<td>0.85</td>
</tr>
<tr>
<td>Anti-Donor HLA Single Antigen Bead Assay</td>
<td>7188 ± 3503</td>
<td>6473 ± 4946</td>
<td>0.51</td>
</tr>
<tr>
<td>Baseline mean fluorescence index (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antidonor Antibody Specificity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Class 1 only</td>
<td>10 (38%)</td>
<td>30 (59%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Anti-Class 2 only</td>
<td>7 (27%)</td>
<td>13 (25%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Anti-Class 1</td>
<td>19 (73%)</td>
<td>38 (75%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Anti-Class 2</td>
<td>16 (62%)</td>
<td>21 (41%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Both Anti-Class 1 and 2</td>
<td>9 (35%)</td>
<td>8 (16%)</td>
<td>0.082</td>
</tr>
<tr>
<td><strong>Pretransplant Plasma Exchange</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients receiving</td>
<td>18 (69%)</td>
<td>35 (69%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Number of PEs (mean ± SD)</td>
<td>4.0 ± 3.6</td>
<td>3.7 ± 3.4</td>
<td>0.76</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th>Category</th>
<th>Eculizumab Group (n=26)</th>
<th>Control Group (n=51)</th>
<th>p value</th>
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<tr>
<td>Follow-up (mean months ± SD, range)</td>
<td>11.9 ± 6.1 (3.0 – 27.5)</td>
<td>48.8 ± 14.1 (7.8 – 69.8)</td>
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<td>Graft Survival at 1 year (n, %)</td>
<td>16/16 (100%)</td>
<td>49/51 (97%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Antibody mediated rejection &lt; 3 months (n, %)</td>
<td>2 (7.7%)</td>
<td>21 (41%)</td>
<td>0.0031</td>
</tr>
<tr>
<td>Patients developing High DSA Levels ≤ 3 months *</td>
<td>13 (50%)</td>
<td>22 (43%)</td>
<td>0.63</td>
</tr>
<tr>
<td>High DSA Biopsies C4d+ (n, %)</td>
<td>13 (100%)</td>
<td>20 (90.9%)</td>
<td>0.52</td>
</tr>
<tr>
<td>High DSA and C4d+ biopsies Showing AMR (n, %)</td>
<td>2 (15%)</td>
<td>20 (100%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cellular Rejection ≤3 months (n, %)</td>
<td>1 (6.2%)</td>
<td>1 (2.0%)</td>
<td>0.42</td>
</tr>
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*Please include the graft loss data in the dataset.
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Histology with High DSA post-TX
BFXM >359 post-transplant

Control
BFXM 550 = AMR

Eculizumab
BFXM 604 = NI
Histology with High DSA post-TX
BFXM >359 post-transplant

Control
BFXM 550 = AMR

Eculizumab
BFXM 604 = NI

N=22 (43%)
All AMR
Histology with High DSA post-TX
BFXM >359 post-transplant

Control
BFXM 550 =AMR

Eculizumab
BFXM 604 =NI

N=22 (43%)
All AMR

N=13 (50%)
2 AMR
Case: Early AMR with Eculizumab

- Elevated creatinine on POD #7 and 14
- Increased DSA
- Biopsy—thrombotic microangiopathy
- Eculizumab level therapeutic with no hemolytic activity
- Both treated with PE, resolved
- Cause unclear?
Plasma Exchange: Post Transplant

- **Control group**
  - BFXM >300 at baseline, 7 d PE per protocol
  - Any AMR

- **Eculizumab group**
  - 1 patient per protocol early
  - 21 patients no PE per protocol
  - 2 patient with AMR
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<td>Post-Transplant PE</td>
<td>3 (12.5%)</td>
<td>39 (76.5%)</td>
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</tr>
<tr>
<td>Splenectomy in patients with AMR</td>
<td>0</td>
<td>9 (17.7%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Graft Dysfunction</td>
<td>0.45 ± 0.37</td>
<td>0.93 ± 1.15</td>
<td>0.0087</td>
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Δ Cr (mg/dl)=Maximum - Nadir in first month
Complications

• All patients receive pretransplant meningococcal vaccine

• No treatment related infections
Stopping Eculizumab
Goal BFXM <200

- No AMR after stopping eculizumab
- 4 weeks: 8 patients stopped
- 9 weeks: 6 stopped
- >9 weeks: 2 continued
  - 2 stopped at 1 year
Chronic Injury: Transplant Glomerulopathy
Minireview

Transplant Glomerulopathy

F. G. Cosio\textsuperscript{a,*,} J. M. Gloor\textsuperscript{a}, S. Sethi\textsuperscript{b} and M. D. Stegall\textsuperscript{b}

\textsuperscript{a}Division of Nephrology and Hypertension, Department of Internal Medicine, \textsuperscript{b}Division of Transplant Surgery, Department of Surgery and \textsuperscript{c}Division of Anatomic Pathology, Department of Pathology, Mayo Clinic and

...view, we will define TG by the characteristic duplication of glomerular basement membrane (GBM) observed by light microscopy (Figure 1), as recommended by the Banff working group (3).

Evidence is accumulating that TG has a unique pathogenesis that distinguishes it from other chronic pathologic con-
## Interesting Cases

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<th>1 yr cg/ci</th>
<th>Cr*</th>
<th>BFXM*</th>
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<td>No</td>
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<td>0/0</td>
<td>1.1</td>
<td>222</td>
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<tr>
<td>#10</td>
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<td>1/2</td>
<td>3.1</td>
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<tr>
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<td>?</td>
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*Most recent or 1 year*
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*Most recent or 1 year*
Late Events:
**Chronic Injury, Graft Loss and Death**

**Transplant Glomerulopathy at 12 months**
- Eculizumab 6.7% (1/15)
- Historical Controls 36% (15/42)

\[ P=0.044 \]

**Graft loss and Death**
- 1 graft loss at 2 years due to TG in eculizumab group
- 1 death due to Burkitt’s lymphoma at 2.5 years
Conclusions:
Terminal complement blockade with eculizumab

- Decreases the incidence of early AMR
- Prevents AMR and graft dysfunction with higher DSA levels post-transplant
- Decreases need for PE and splenectomy
- Decreased TG at 1 year?
- Chronic changes may require additional therapy
Therapeutic Options

Highly Sensitized Patient

- DSA-negative Living Donor or Paired Donation
- Living Donor Desensitization With Eculizumab
- Deceased Donor With Eculizumab