Update on Treatment Options for Antibody-Mediated Rejection

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Introduction-Rejection

• Over the last decade, incidence of classic T cell-mediated acute renal allograft rejection has decreased dramatically

• Long-term renal allograft survival has not improved in a commensurate fashion compared to the improvements noted with 1-year acute rejection rates
Introduction

- Antibody mediated rejection or “humoral” rejection was recognized early in the history of transplantation as hyperacute rejection caused by the presence of preformed antibodies to blood group ABO or HLA antigens.
- Introduction of pre-transplant cross match techniques and use of ABO compatible donors has essentially eliminated hyperacute rejection.
Introduction

• The detection of C4d (a degradation product of the classic complement pathway) allowed for the recognition of the clinical relevance of alloantibodies, beyond their historical role as mediators of hyperacute rejection.
# AMR Renal Transplant Pathology

Table 1. Antibody-mediated renal transplant pathology

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical Presentation</th>
<th>Histology</th>
<th>C4d</th>
<th>Serology</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute rejection</td>
<td>Immediate graft failure (minutes to hours) after reperfusion</td>
<td>Neutrophils in glomeruli and PTC; hemorrhage, necrosis, thrombosis</td>
<td>Positive PTC; may be negative early</td>
<td>Anti-donor HLA or ABO positive in majority</td>
<td>Almost always irreversible</td>
</tr>
<tr>
<td>Acute humoral rejection</td>
<td>Rapid loss of graft function (days), any time after transplantation</td>
<td>Variable. Neutrophils and macrophages in glomeruli and PTC; fibrinoid arterial necrosis, acute tubular injury; ± cell-mediated rejection</td>
<td>Positive PTC; variable glomeruli</td>
<td>Anti-donor HLA (class I and/or II) or ABO positive in majority (approximately 90%)</td>
<td>Often reversible with appropriate treatment</td>
</tr>
<tr>
<td>Chronic humoral rejection</td>
<td>Slow, progressive loss of graft function (months to years), often with proteinuria, hypertension</td>
<td>GBM duplication; mononuclear cells in glomeruli and PTC; intimal fibrosis; tubular atrophy and interstitial fibrosis; PTC basement membrane multilamination (by EM)</td>
<td>Positive PTC (often patchy); glomeruli variably positive; occasionally only glomeruli positive</td>
<td>Anti-donor HLA positive in majority, especially to MHC class II antigens.</td>
<td>Outcome and optimal therapy not yet defined</td>
</tr>
<tr>
<td>Accommodation</td>
<td>Normal graft function</td>
<td>Normal, or minor changes</td>
<td>Positive PTC; variable glomeruli</td>
<td>Common with ABO incompatibility; occasionally with HLA antibodies</td>
<td>Outcome and optimal therapy not yet defined</td>
</tr>
</tbody>
</table>

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*a EM, electron microscopy; GBM, glomerular basement membrane; PTC, peritubular capillary.
Banff Classification- Acute Antibody Mediated Rejection Criteria

• Consists of 3 cardinal features
  • 1) morphologic evidence of tissue injury
    • Type I: ATN-like, minimal inflammation
    • Type II: capillary-glomerulitis, PMN and/or mononuclear leukocytes in PTC and/or thrombosis
    • Type III: arterial-transmural inflammation/ fibrinoid changes
  
  • 2) Immunopathologic evidence for antibody-mediated action
    • C4d deposition of the peritubular capillaries that can be diffuse or focal

  • 3) Serologic evidence of circulating antibodies to donor HLA or to other donor endothelial antigens
C4d staining of intertubular capillaries—evidence for acute humoral rejection
Histopathologic Evidence
Antibody Mediated Rejection—Incidence and Prognosis

• Antibody mediated rejection resulting in graft dysfunction is estimated to occur in 3 to 10 percent of all renal transplants
• It is estimated that as much as 30% of acute rejection episodes noted today have an antibody component
• In general: antibody-mediated immunologic processes portend a worse prognosis
  • Lederer et al reported a 4 year 50% graft survival for C4d+ patients compared with an 8 year 50% graft survival for C4d negative patients
  • Poduval et al reported a one year graft loss of 65% for grafts with diffuse C4d + diagnosis compared with 33% for focal and negative C4d grafts
• In addition- recent studies including the DeKaf study suggest that chronic immune injury mediated by anti-donor antibodies may account for the majority of graft losses
Targeting Antibodies in Transplantation
Traditional Therapies

• **Plasmapheresis**
  - Acutely depletes anti-human leukocyte antigen antibodies—only a temporizing measure—limited by rebound of antibodies post-pheresis, must be used in conjunction with other therapies

• **IVIG**
  - Neutralizes circulating alloantibody
  - Inhibits complement activation
  - Modulates cell-mediated immunity through Fc receptors

• **Rituximab**
  - Chimeric anti-CD20 monoclonal antibody targets B cells
  - Depletion of B cells through complement-dependent cytotoxicity and antibody dependent cellular toxicity and promotion of apoptosis
Targeting Antibodies in Transplantation
<table>
<thead>
<tr>
<th>No.</th>
<th>Category</th>
<th>Treatment</th>
<th>Major mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>Cyclosporin A</td>
<td>Indirectly inhibit B cell proliferation secondary to reduced cytokine production by T cells</td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>Tacrolimus (FK506)</td>
<td>Indirectly inhibit B cell proliferation secondary to reduced cytokine production by T cells</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>Rapamycin (sirolimus)</td>
<td>Indirectly inhibit B cell proliferation secondary to reduced cytokine production by T cells</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>Azathioprine</td>
<td>Inhibit DNA synthesis in dividing cells (T, B and other dividing cells)</td>
</tr>
<tr>
<td>5</td>
<td>I</td>
<td>Cyclophosphamide</td>
<td>Inhibit DNA synthesis in dividing cells (T, B and other dividing cells)</td>
</tr>
<tr>
<td>6</td>
<td>I</td>
<td>Mycophenolate mofetil (MMF)</td>
<td>Inhibit DNA synthesis in dividing cells (mainly T and B cells)</td>
</tr>
<tr>
<td>7</td>
<td>I</td>
<td>Rituximab</td>
<td>Anti-CD-20 (B cell surface marker) mAb, deplete B cells</td>
</tr>
<tr>
<td>8</td>
<td>I</td>
<td>OKT3</td>
<td>Anti-CD3 (T-cell surface marker) antibody, indirectly inhibit B-cell proliferation</td>
</tr>
<tr>
<td>9</td>
<td>I</td>
<td>Anti-thymocyte globulin (ATG) and anti-lymphocyte globulin (ALG)</td>
<td>Directly deplete or indirectly inhibit B cells</td>
</tr>
<tr>
<td>10</td>
<td>I</td>
<td>Campath-1H</td>
<td>Anti-CD52 (surface marker of thymocytes, T, B cells, etc.), direct deplete B cells</td>
</tr>
<tr>
<td>11</td>
<td>I</td>
<td>Splenectomy</td>
<td>Surgically remove lymphocyte-producing organ (both B and T)</td>
</tr>
<tr>
<td>12</td>
<td>II</td>
<td>Immunoadsorption</td>
<td>Remove antibody from periphery (blood group antigen-, protein A- or anti-human Ig antibody-coated columns)</td>
</tr>
<tr>
<td>13</td>
<td>II</td>
<td>Plasmapheresis (PPH) or plasma exchange (PE)</td>
<td>Remove antibodies and other humoral factors (complements, cytokines, etc.) from periphery</td>
</tr>
<tr>
<td>14</td>
<td>II</td>
<td>Intravenous immunoglobulin (IVIG)</td>
<td>Anti-idiotypic effects (blocking of the antigen-binding cites of anti-donor antibodies) and others</td>
</tr>
<tr>
<td>15</td>
<td>III</td>
<td>Anticoagulation therapy</td>
<td>Inhibit the formation of clot (Figure 1A)</td>
</tr>
<tr>
<td>16</td>
<td>III and I</td>
<td>Glucocorticoid</td>
<td>Anti-inflammatory effects (Figure 1.1 and D), B-cell apoptosis</td>
</tr>
</tbody>
</table>

*1 = inhibition and depletion of antibody-producing cells; II = removal or blocking of preexisting or newly developed antibodies; III = impediment or postponement of antibody-mediated primary and secondary tissue injury.
Novel B cell targets

• Third generation CD20-specific mAbs (to decrease potential immunogenicity)
  • Ocrelizumab
  • Ofatumumab
  • Epratuzumab- humanized mAb targeting CD22- mature B cell receptor

• B-cell activating factors (BAFF)
  • Tumor-necrosis factor-family ligands act as anti-apoptotic survival factors critical for maturation of the B-cell lineage
    • Belimumab
    • Atacicept
Novel Therapeutics for Treatment of AMR
Bortezomib

- A selective inhibitor of the 26S Proteasome - approved for the treatment of multiple myeloma
  - Induces apoptosis of rapidly dividing, metabolically active cells with extensive protein synthesis, including normal plasma cells
Proteins are targeted to the 26S proteasome for degradation by a process of polyubiquitination. Bortezomib inhibits the catalytic activity of the proteasome, thus preventing proteolysis. Ub denotes ubiquitin.
Targeting Antibodies in Transplantation

Graft

- Donor MHC I and MHC II
- Alloantibody
- C3 convertase
- C5b
- MAC
- C1 complex

Complement inhibitors

Proteasome inhibitors

CD4+ T cell

- CD28
- TCR
- CD40L

B cell

- BCR
- CD20
- BAFF-R
- BCMA
- TACI

Anti-CD40

Anti-CD20

BAFF inhibitors

CD28/B7 blockade
Bortezomib

- In a case series, Everly et al treated 6 patients with mixed ACR or AMR refractory to current therapies with a single cycle of bortezomib (four administrations of 1.3 g/m2 over 11 days).
- In all patients bortezomib reversed the rejection, improved renal function, and decreased DSA.
- Recently, Waiser et al compared bortezomib and rituximab (in addition to PP, IVIG, and Steroids) and found treatment with bortezomib to be partially effective (graft survival 18 months), while treatment with Rituximab was not.
- No randomized control trials.
- Always used in conjunction with other therapies.
- Neuropathy.
Eculizumab

- Humanized monoclonal antibody directed against complement protein C5
- FDA approved for the treatment of Paroxysmal Nocturnal Hemoglobinuria and recently, atypical HUS

*Figure 1. Complement activation pathways. The classic pathway is relevant to antibody-mediated rejection. The other pathways have not been shown to participate in acute or chronic rejection. C4d remains covalently bound in the tissue for several days after complement activation (see text). Adapted from reference (6), with permission.*
Eculizumab

- Many case reports demonstrate a role for eculizumab in treatment of AMR
- Prospective study compared the outcomes of using eculizumab to prevent AMR and TG after transplantation in a series of HLA-sensitized pre-transplant positive-FXM patients (n=26)
  - Incidence of AMR at 3 months was 7.7% compared to a historical control group (41.2%)
  - Incidence of TG at one year was low (6.7%) in eculizumab group versus 35.7% historical control
  - Multicenter trial in progress
Eculizumab- UCSF Case Report
Eculizumab for the Treatment of *De Novo* Thrombotic Microangiopathy Post Simultaneous Pancreas-Kidney Transplantation—a Case Report

- 34 year old female with ESRD secondary to Type I DM s/p SPK who presented POD 8 with Acute kidney injury, anemia, thrombocytopenia.
- Kidney biopsy revealed AMR and evidence for thrombotic microangiopathy
- DSA’s were positive
Thank You!