KIDNEY TRANSPLANT REJECTION AND BELATACEPT

Sushma Bhusal
Nephrology Fellow
3.29.16
Case presentation

- 43 yo AAF with h/o SLE, lupus nephritis, s/p LURT in 1/2011, graft failure, presently on dialysis, presented with altered mental status and fatigue x 1 day

- **HPI**
  - Had been in her usual state of health until 1 day prior
  - On the way to the hospital developed episode of unresponsiveness and abnormal movements
Case presentation

**PMH**

- SLE
- Lupus nephritis
- ESRD S/P transplant
- Acute rejection
- Uncontrolled DM2
- HTN
- Pancytopenia

**PSH**

- LURT (husband) 1/2011
Case presentation

- **Allergies:** NKDA

- **SH:** no illicits, non smoker, non alcoholic

- **FH:** non contributory
Medications

- Amlodipine 10 mg po d
- Coreg 25 mg bid
- Calcium carbonate/vit d3 po bid
- Folic acid 1 mg po d
- Prednisone 5 mg po d
- Lantus 15 units sc qhs
- Simvastatin 10 mg hs
- Dapsone 100 mg po daily
- Ferrous sulfate 325 mg bid
Physical exam

- Vitals: BP 140-180/90S, HR 70-80s, RR 18, O2 sat 100% RA
- Gen: sleepy, resting in bed in NAD
- HEENT: PERRL, EOMI, slightly dry mucous membranes
- Neck: no elevated JVP
- CV: RRR, normal S1S2, no m/r/g
- Chest: right sided permacath c/d/i. Lungs CTA bilaterally
- Abd: soft nontender nondistended
- Ext: no LE edema, wwp
- Neuro: no focal neurologic deficits. Axox3
LABS

LFTs: AST/ALT: 31/47, ALP 147, T bil 0.5, Albumin 4.6
C3/C4: normal

- **CSF:** Normal
- **CXR:** Right permacath tip in right atrium.
  No focal infiltrate. Interim increased pulmonary vascular congestion
- **CT HEAD:** NORMAL
Hospital course

- Patient underwent LP, head CT: all normal
- Neuro consulted: keppra given, VEEG normal
- Seizures thought to be from hyperglycemia
- Keppra discontinued, patient discharged home
Case presentation: Timeline of renal disease

1/2011: Underwent uneventful renal biopsy, donor husband, Cr down trended to 0.9-1

3/2011:
- Cr elevated to 1.4, renal biopsy done, normal biopsy
- Uncontrolled glucose, Pred every other day, switched FK to everolimus 3/13/2013
- Cr down to baseline

5/2013
- Cr increased to 1.9, T-cell mediated rejection, moderate, Banff 1b on biopsy, immune complex mediated glomerulonephritis, low grade
- treated with solumedrol 500 mg x 2, taper Pred, everolimus and FK both continued with increments in prograf dose

6/2013
- Prograf level 26.6, Cr upto 2.2, Prograf held
- Cr rise thought to be from CNI toxicity
Case presentation: Timeline of renal disease

- **9/2013:**
  - Cr initial downward trend, then rise:
  - Biopsy undertaken: interstitial fibrosis and tubular atrophy (40-60%), no evidence of any specific etiology (previous term chronic allograft nephropathy)
  - complete foot process effacement, persistent immune complex mediated glomerulonephritis, low grade
  - Cholesterol increased: belatacept considered
Case presentation: Timeline of renal disease

6/2014

- Cr to 3.6, admitted for belatacept, underwent renal biopsy, everolimus stopped
- Mild acute rejection, IF/TA 50-60%
- Treated with Solumedrol

7/2014-10/2015

- Cr continued to rise: belatacept started 7/16/14, q 2 weeks initially, prograf tapered off
- Developed pancytopenia, cellcept held
- Belatacept continued until 7/2015
- Dialysis started on 10/2015
Outline

• Mechanisms of rejection
• TCR signaling
• Belatacept in Renal transplant
Mechanisms of Rejection

• Innate immunity

• Adaptive immunity
Innate immunity

• Represents the first step in rejection mechanisms

• Guides the development of adaptive immune response

• 1989:
  • Janeway postulated non-self-recognition initiated pattern recognition receptors PRRs
  • PRRs recognize PAMPs (LPS/peptidoglycan) \( \rightarrow \) production of several pro-inflammatory mediators that mediate initial inflammatory response and guide subsequent adaptive immune response

• 1990s: Matzinger. PRRs recognize as danger signals also self molecules that are released from dying or necrotic cells (DAMPs) in injured graft

Ponticelli et al. Nephron 2015
Kuo et al. J of Transplantation 2010
What are DAMPs

- Substances released from damaged or necrotic tissues that can be recognized by specific receptors of innate immunity (PRRs)

- Several DAMPs are recognized:
  - Heat-shock protein 60 (Hsp60)
  - Hsp70
  - High mobility-group box 1 protein (HMGB1)
  - Surfactant protein A
  - β-defensin 2
  - ECM proteins: hyaluronan, fibronectin and Heparan sulfate
What are DAMPs

- In context of transplant
  - Brain deceased donor
  - Organ procurement
  - Ischemia–Reperfusion

- Ag-independent insults to the allograft caused by procurement and ischemia/reperfusion injury enhance immunogenicity through the activation of passenger APCs

Goto et al. Transplantation 2012
Ponticelli et al. Nephron 2015
Kuo et al. J of Transplantation 2010
DAMPs are recognized by PRRs

- Toll like receptors
- NOD like receptors
  - NOD1/2
  - NRLP3
- RAGE

Goto et al. Transplantation 2012
Ponticelli et al. Nephron 2015
Kuo et al. J of Transplantation 2010
Maturation of DCs

Ponticelli et al. Nephron 2015
Adaptive Immunity

• Cellular
  • Ag presentation
  • Ag recognition
  • T cell activation

• Humoral
Antigen Presentation
Antigen presentation and Recognition

Nankivell et al. NEJM 2010
Co-stimulation
T Cell activation and differentiation
BELATACEPT
A Phase III Study of Belatacept-based Immunosuppression Regimens versus Cyclosporine in Renal Transplant Recipients (BENEFIT Study)
BENEFIT Trials

• **Patients:** adults receiving a kidney transplant from living or standard criteria deceased donors

• **Randomized** to MI belatacept, LI belatacept and cyclosporine

• **Co-primary endpoints at 12 months**
  • Patient/graft survival, a composite
  • Renal impairment endpoint (% with mGFR<60 ml/min/1.73m² at month 12 or a decrease in mGFR ≥10 ml/min/1.73 m² month 3–month 12)
  • Incidence of acute rejection

• **Secondary endpoints**
  • Mean measured glomerular filtration rate,
  • Mean calculated glomerular filtration rate using MDRD equation
  • Prevalence of chronic allograft nephropathy on protocol biopsies at week 52
Table 2: Outcomes: Patient/graft survival, renal function and structure and acute rejection

<table>
<thead>
<tr>
<th>Month 12 endpoints</th>
<th>Belatacept MI (n = 219)</th>
<th>Belatacept LI (n = 226)</th>
<th>Cyclosporine (n = 221)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient/graft survival</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Patients surviving with functioning graft, n (%)</td>
<td>209 (95)</td>
<td>218 (97)</td>
<td>206 (93)</td>
</tr>
<tr>
<td>95% CI</td>
<td>92.7–99.2</td>
<td>94.1–99.9</td>
<td>99.9–99.5</td>
</tr>
<tr>
<td>Difference from CsA (97.3% CI)</td>
<td>2.2 (–2.9, 7.5)</td>
<td>3.2 (–1.5, 8.4)</td>
<td>–</td>
</tr>
<tr>
<td>Graft loss or death, n (%)</td>
<td>10 (5)</td>
<td>8 (4)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Graft loss</td>
<td>4 (2)</td>
<td>5 (2)</td>
<td>0 (4)</td>
</tr>
<tr>
<td>Death</td>
<td>6 (3)</td>
<td>4 (2)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Death with functioning graft</td>
<td>6 (3)</td>
<td>3 (1)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Imputed as graft loss or death, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Renal function and structure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGFR &lt;60 mL/min/1.73 m² or decrease</td>
<td>115 (55)</td>
<td>116 (54)</td>
<td>166 (78)</td>
</tr>
<tr>
<td>Month 3–12 &lt;10 mL/min/1.73 m², n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>48.3–51.8</td>
<td>47.5–50.9</td>
<td>72.4–83.5</td>
</tr>
<tr>
<td>Difference from CsA (97.3% CI)</td>
<td>–22.9 (–32.6, –12.9)</td>
<td>–23.7 (–33.3, –13.7)</td>
<td>–</td>
</tr>
<tr>
<td>p-Value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>–</td>
</tr>
<tr>
<td>Mean mGFR, mL/min/1.73 m² [SD]</td>
<td>65.0 (30.0)</td>
<td>63.4 (27.7)</td>
<td>50.4 (18.7)</td>
</tr>
<tr>
<td>Estimated difference from CsA (97.3% CI)</td>
<td>14.6 (8.8, 20.3)</td>
<td>12.9 (7.2, 18.8)</td>
<td>–</td>
</tr>
<tr>
<td>p-Value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>–</td>
</tr>
<tr>
<td>CAN, n (%) [95% CI]</td>
<td>40 (18 [13.1–23.4])</td>
<td>54 (24 [18.3–29.5])</td>
<td>71 (32 [26.2–38.6])</td>
</tr>
<tr>
<td>Difference from CsA (97.3% CI)</td>
<td>–14.2 (–23.2, –5.0)</td>
<td>–8.5 (–17.9, 0.9)</td>
<td>–</td>
</tr>
<tr>
<td>Mild CAN (stage I), n (%)</td>
<td>21 (10)</td>
<td>29 (13)</td>
<td>41 (19)</td>
</tr>
<tr>
<td>Moderate CAN (stage II), n (%)</td>
<td>5 (2)</td>
<td>6 (3)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Severe CAN (stage III), n (%)</td>
<td>4 (2)</td>
<td>6 (3)</td>
<td>6 (3)</td>
</tr>
<tr>
<td><strong>Acute rejection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute rejection, n (%)</td>
<td>49 (22)</td>
<td>39 (17)</td>
<td>16 (7)</td>
</tr>
<tr>
<td>95% CI</td>
<td>16.9–27.9</td>
<td>12.3–22.2</td>
<td>3.8–10.7</td>
</tr>
<tr>
<td>Difference from CsA (97.3% CI)</td>
<td>15.1 (7.9, 22.7)</td>
<td>10.0 (3.3, 17.1)</td>
<td>–</td>
</tr>
<tr>
<td>Banff grade, n (%)</td>
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<td></td>
<td></td>
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<tr>
<td>Mild acute (Ia)</td>
<td>7 (3)</td>
<td>4 (2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Mild acute (Ib)</td>
<td>3 (1)</td>
<td>8 (4)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Moderate acute (IIa)</td>
<td>17 (8)</td>
<td>16 (7)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Moderate acute (IIb)</td>
<td>20 (9)</td>
<td>10 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Severe acute (III)</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>
• Higher incidence (MI: 22%, LI: 17% and cyclosporine: 7%) and grade of acute rejection episodes with belatacept

• Safety generally similar but more PTLD (1 pt in MI, 2 in LI and 1 in cyclo group)
Three-Year Outcomes from BENEFIT, a Randomized, Active-Controlled, Parallel-Group Study in Adult Kidney Transplant Recipients
BENEFIT 2012: 3 year follow up results

• 471/666 patients completed ≥3 years of therapy

• Similar patient/graft survival rates (92% (MI), 92% (LI), and 89% (cyclosporine)

• Mean calculated GFR ~21 ml/min/1.73 m2 higher in the belatacept versus cyclosporine at year 3

• No new safety signals or PTLD after month 18 (2 patients in MI belatacept had developed PTLD > 12 months)
A Phase III Study of Belatacept Versus Cyclosporine in Kidney Transplants from Extended Criteria Donors (BENEFIT-EXT Study)

Three-Year Outcomes From BENEFIT-EXT: A Phase III Study of Belatacept Versus Cyclosporine in Recipients of Extended Criteria Donor Kidneys
BENEFIT: EXT Results

**Results**
- Similar patient/graft survival and acute rejection rates
- Better renal function
- Improvement in the cardiovascular/metabolic risk profile
- Increased incidence of PTLD

**3 yr follow up:**
- PTLD and tuberculosis higher, all other end points similar
Original Article

Belatacept and Long-Term Outcomes in Kidney Transplantation

Flavio Vincenti, M.D., Lionel Rostaing, M.D., Ph.D., Joseph Grinyo, M.D., Ph.D., Kim Rice, M.D., Steven Steinberg, M.D., Luis Gaite, M.D., Marie-Christine Moal, M.D., Guillermo A. Mondragon-Ramirez, M.D., Jatin Kothari, M.D., Martin S. Polinsky, M.D., Herwig-Ulf Meier-Kriesche, M.D., Stephane Munier, M.Sc., and Christian P. Larsen, M.D., Ph.D.
Results

• Followed up for 84 months (7 years)
  • 153/219 patients treated with MI belatacept regimen
  • 163/226 treated with LI regimen
  • 131/215 treated with the cyclosporine

• 43% reduction in the risk of death or graft loss observed for both the more-intensive (HR : 0.57; 95% CI : 0.35 TO 0.95; P = 0.02) and LI (HR: 0.57; 95% CI, 0.35 TO 0.94; P = 0.02) vs Cyclosporine

• The mean eGFR increased over 7-year period with both belatacept regimens but declined with the cyclosporine regimen.

• The cumulative frequencies of serious adverse events at month 84 were similar across treatment groups.
I am 3 and a half months already !!!!!