Better than Google-
Click on Immunosuppression
Renal Transplant

David Landsberg
Oct 3 2008
OUTLINE

• History of Immunosuppression
• Trends in Immunosuppression
  – FK vs CYA
  – Steroid Minimization
  – CNI Avoidance
  – Sirolimus / Everolimus
• Individualization
• New Agents
HISTORY OF IMMUNOSUPPRESSION

• 1960s  Imuran/Prednisone
• 1970s  Imuran/Prednisone/ALG
• 1980s  Cyclosporine/OKT3
• Early 1990s  Tacrolimus
• mid 1990s  Mycophenolate
• late 1990s  IL2-Receptor Blockers
              Sirolimus / Everolimus
• 2000    Rituximab /Alemtuzumab
• 2002    Belatacept / FTY 720
Outcomes of Renal Allografts

- Radiation
- Prednisone
- 6-MP
- Cyclosporine Emulsion
- Tacrolimus
- MMF
- Daclizumab
- Basiliximab
- Thymoglobulin
- Sirolimus

Rejection <12 mo

1 Year Survival

Year

Percent
Trends in Immunosuppression

- Tacrolimus vs Cyclosporine
- Steroid Minimization
- CNI Avoidance
- Induction
Cyclosporine and Tacrolimus: Calcineurin Inhibitors

- TCR complex (αβ TCR, CD3, CD4, etc)
- Costimulatory molecules (i.e., CD28 and CD40L)
- IL-2
- IL-2R (α, CD25 (inducible))
- IL-2 gene
- Cyclosporine: Cyclophilin
- Tacrolimus: FKBP
- Calmodulin
- Calcineurin
- Phosphatase activity
- Kinase activity
- Calmodulin: Calcineurin
- Apoptosis
- De novo purine synthesis
- TOR
- G1 → S → M → G2
- CD25 (inducible)
## CsA vs FK506: Side Effects

<table>
<thead>
<tr>
<th></th>
<th>CsA</th>
<th>FK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>nephrotoxicity</strong></td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>hypertension</strong></td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>neurotoxicity</strong></td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>(tremor/seizures/convulsions)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>hyperglycemia/diabetes</strong></td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td><strong>electrolyte disorders</strong></td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>(hypoK/hyperK/hypoMg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Steroid Minimization

• Withdrawal
• Complete Avoidance
• Periop only
• Early withdrawal
Steroid Withdrawal

- All withdrawal studies have shown higher risk of acute rejection
- Low dose long-term steroid may reduce risk of chronic rejection
- No long-term advantage to late steroid withdrawal versus low dose in terms of the usual steroid complications
Target Groups for Steroid Avoidance

- Previous large exposure
- Children
- Low BMD
- Preexisting atherosclerotic disease
- Risk for hyperglycemia or hyperlipidemia
Immunosuppressive Protocols for Steroid Minimization

- Antibody (anti CD 25, anti CD3, anti CD 52 or ATG)
- CNI or Sirolimus
- Mycophenolate
FREEDOM TRIAL
American Journal of Transplantation
2008; 8: 307–316

• 3 arms
  • no steroid
  • steroid withdrawal by 7 days
  • standard therapy

• Cyclosporine
• Enteric Coated Mycophenolate Sodium
• Simulect
## FREEDOM TRIAL

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>12 month GFR</th>
<th>Acute Rej</th>
</tr>
</thead>
<tbody>
<tr>
<td>no Steroids</td>
<td>111</td>
<td>64.7</td>
<td>31.5%</td>
</tr>
<tr>
<td>Steroids to day 7</td>
<td>115</td>
<td>61.6</td>
<td>26.1%</td>
</tr>
<tr>
<td>Standard Steroids</td>
<td>109</td>
<td>63.4</td>
<td>14.7%</td>
</tr>
</tbody>
</table>
Freedom – Benefits of Steroid Avoidance

• Less diabetes
• Better Lipids
• Less Weight Gain
• Better BMD
Astellas Steroid Withdrawal Trial

- Multicentre 500 patients
- Double blinded placebo controlled trial
- 7 day steroid withdrawal versus standard therapy
- Tacrolimus, MMF and ATG or IL-2R antibody
Astellas Steroid Withdrawal Trial

- no differences seen at 3 years
- trend to more acute rejection 16.2% vs 9.7%
- no striking differences in “steroid related” complications including diabetes
Can we eliminate calcineurin inhibitors?
US DeNovo Maintenance Regimens for Kidney Transplant Recipients

- 49% FK/MMF/P
- 21% CsA/MMF/P
- 20% Others
- 5% Rapa/MMF/P
- 2% Rapa/FK/P
- 3% Rapa/CsA/P

UNOS: 11/02
Calcineurin Inhibitors
Elimination

• Avoidance
  – Sirolimus/MMF

• Withdrawal
  – CYA / Sirolimus

• Sparing
Mycophenolate Mofetil/Sirolimus Compared to Other Common Immunosuppressive Regimens in Kidney Transplantation


<table>
<thead>
<tr>
<th>Regimen</th>
<th>Acute Rejection</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FK/MMF</td>
<td>ref</td>
<td>-</td>
</tr>
<tr>
<td>CSA/MMF</td>
<td>1.16</td>
<td>1.09-1.24</td>
</tr>
<tr>
<td>FK/SRL</td>
<td>0.92</td>
<td>0.82-1.03</td>
</tr>
<tr>
<td>CYA/SRL</td>
<td>1.01</td>
<td>0.87-1.17</td>
</tr>
<tr>
<td>SRL/MMF</td>
<td>1.53</td>
<td>1.33-1.75</td>
</tr>
</tbody>
</table>
Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation
The Symphony Trial

Prospective randomized 4 arm trial with 1645 patients enrolled

1. Standard dose CYA, MMF, Steroid
2. Daclizumab, reduced dose Tac, MMF, Steroid
3. Daclizumab, reduced dose CYA, MMF, Steroid
4. Dalizumab, Sirolimus, MMF, Steroid
Cumulative Probability of Biopsy-Proven Acute Rejection (Panel A) and Allograft Survival (Panel B), According to Study Group

Conclusion

• A regimen of daclizumab, mycophenolate mofetil, and corticosteroids in combination with low-dose tacrolimus may be advantageous for renal function, allograft survival, and acute rejection rates, as compared with regimens containing daclizumab induction plus either low-dose cyclosporine or low-dose sirolimus or with standard-dose cyclosporine without induction
## Sirolimus and Everolimus

<table>
<thead>
<tr>
<th><strong>Pros</strong></th>
<th><strong>Cons</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Not nephrotoxic</td>
<td>• Delayed wound healing</td>
</tr>
<tr>
<td>• Once daily dosing</td>
<td>• Hyperlipidemias</td>
</tr>
<tr>
<td>• Can be used without CNI’s but not early</td>
<td>• Proteinuria</td>
</tr>
<tr>
<td>• ? anti neoplastic characteristics</td>
<td>• Brochiolitis Obliterans</td>
</tr>
<tr>
<td>• ? Anti atherosclerotic</td>
<td>• Expense</td>
</tr>
<tr>
<td></td>
<td>• Drug monitoring</td>
</tr>
</tbody>
</table>
RATIONALE FOR INDIVIDUALIZING IMMUNOSUPPRESSION

Too Much
- Cardiovascular Disease
- Infection
- Neoplasia
- Nephrotoxicity

Too Little
- Allograft Rejection
INDIVIDUALIZING IMMUNOSUPPRESSION BASED ON IMMUNOLOGIC RISK

PRE-TRANSPLANT IMMUNOMODULATION

INDUCTION ANTIBODY THERAPY TRIPLE THERAPY MAINTENANCE

MINIMIZATION PROTOCOLS

HIGH RISK
- HIGHLY SENSITIZED
- NON-PRIMARY TRANSPLANT
- AFRICAN AMERICAN/HISPANIC ETHNICITY
- CADAVERIC DONOR SOURCE
- POOR HLA MATCH

LOW RISK
- NONSENSITIZED
- ASIAN/CAUCASIAN ETHNICITY
- THE ELDERLY
- LIVING DONOR SOURCE
- GOOD HLA MATCH
**Immunosuppression: Long-Term Side Effects that Enhance Cardiovascular Risk**

<table>
<thead>
<tr>
<th>Condition</th>
<th>CsA</th>
<th>Tac</th>
<th>SRL</th>
<th>Ster</th>
<th>MMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>++</td>
<td>+</td>
<td>Ø</td>
<td>++</td>
<td>Ø</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>+</td>
<td>++</td>
<td>Ø</td>
<td>+++</td>
<td>Ø</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>++</td>
<td>++</td>
<td>Ø</td>
<td>Ø</td>
<td>Ø</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>Ø</td>
</tr>
</tbody>
</table>

CsA = cyclosporine; Tac = tacrolimus; SRL = sirolimus; Ster = corticosteroids; MMF = mycophenolate mofetil

+++ = severe; + = mild; ++ = moderate; Ø = none;
Current Immunosuppressive Low Risk Protocol

- Basilixumab 20mg. Day 0 and 4
- MMF 1 gram bid
- CNI
- Perioperative Steroids
New Agents

- FTY 720
- Alemtuzumab
- Belatacept
- Efalizumab
- Rituximab
- FK 778
- ISA 247
- AEB071
- CP690550
Individual Immunosuppressive Drugs and Sites of Action in the Three-Signal Model

<table>
<thead>
<tr>
<th>Immune Response Antigens</th>
<th>Adhesion &amp; Cell Trafficking</th>
<th>Heterogeneous Pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD1a</td>
<td>CD6</td>
<td>CD2</td>
</tr>
<tr>
<td>CD3/TCR</td>
<td>CD11a/CD18 (LFA-1)</td>
<td>CD5</td>
</tr>
<tr>
<td>CD4</td>
<td>CD44</td>
<td>CD11b</td>
</tr>
<tr>
<td>CD6</td>
<td>CD49/CD29 (VLA-4)</td>
<td>CD29</td>
</tr>
<tr>
<td>CD7</td>
<td>CD50 (ICAM-3)</td>
<td>CD38</td>
</tr>
<tr>
<td>CD8</td>
<td>CD51/61</td>
<td>CD40</td>
</tr>
<tr>
<td>CD16</td>
<td>CD54 (ICAM-1)</td>
<td>CD45</td>
</tr>
<tr>
<td>CD19</td>
<td>CD56*</td>
<td>CD52</td>
</tr>
<tr>
<td>CD20*</td>
<td>CD58 (LFA-3)</td>
<td>CD95</td>
</tr>
<tr>
<td>CD25*</td>
<td>LPAM-1(α4β7)</td>
<td>CD126</td>
</tr>
<tr>
<td></td>
<td>CD102 (ICAM-2)</td>
<td>CD138</td>
</tr>
<tr>
<td></td>
<td>CD195 (CCR5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD197 (CCR7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD184 (CXCR4)</td>
<td></td>
</tr>
</tbody>
</table>

**Target Antigens**

**Immune Response Antigens**
- CD1a
- CD3/TCR
- CD4
- CD6
- CD7
- CD8
- CD16
- CD19
- CD20*
- CD25*

**Adhesion & Cell Trafficking**
- CD6
- CD11a/CD18 (LFA-1)
- CD44
- CD49/CD29 (VLA-4)
- CD50 (ICAM-3)
- CD51/61
- CD54 (ICAM-1)
- CD56*
- CD58 (LFA-3)
- LPAM-1(α4β7)
- CD102 (ICAM-2)
- CD195 (CCR5)
- CD197 (CCR7)
- CD184 (CXCR4)

**Heterogeneous Pathways**
- CD2
- CD5
- CD11b
- CD29
- CD38
- CD40
- CD45
- CD52
- CD95
- CD126
- CD138
FTY720

• Novel immunosuppressant which is a spingosine 1-phosphate receptor agonist (S1P)
• S1P receptor agonists induce sequestration of lymphocytes in secondary lymphatic tissue
• Several phase 1/2 studies have shown efficacy
• Phase 3 trial discontinued early because of toxicity
• Is this another way of inducing lymphocyte depletion?
Alemtuzumab

- Humanized anti-CD 52 IgG1 monoclonal antibody.
- Complement fixing so cytotoxic and lymphodepleting
- Profoundly depletes T cells and to a lesser extent
- B cells, natural killer cells and monocytes
Alemtuzumab

• Unlike other agents discussed alemtuzumab is not approved for use in kidney transplantation
• Despite this in 2006 10% of US transplant centres used it as an induction agent.
• Proposed advantages:
  – Tolerogenic
  – CNI sparing
  – Steroid sparing
  – Less expensive
• Absolute lack of controlled trials (more than 400 reports less than 5 randomized prospective)
# Published Effects Of Alemtuzumab

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toletrance Induction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>With DSG</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Near Tolerance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CYA</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Effective with Non-CNI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirolimus alone</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Sirolimus / MMF</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>MMF alone</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Effective with CNI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>steroid sparing</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CNI sparing</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Effective to Treat Rejection</strong></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Belatacept

- Selective costimulation blocker
- Binds surface costimulatory ligands CD 80 and CD 86 of APC
- Interferes with signal 2 by preventing interaction with CD 28 the costimulatory surface receptor of the T cell
### Incidence of Primary and Secondary Efficacy End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Intensive Belatacept (N=74)</th>
<th>Less-Intensive Belatacept (N=71)</th>
<th>Cyclosporine (N=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary efficacy end point</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically suspected and biopsy-proven acute rejection at 6 mo — no. (%)</td>
<td>5 (7)</td>
<td>4 (6)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Absolute difference in rate from cyclosporine group — percentage points (exact 95% CI)*</td>
<td>-1.5 (-11.3 to 8.3)</td>
<td>-2.6 (-12.3 to 6.7)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Secondary efficacy end points</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild acute rejection (grade IA) — no. (%)</td>
<td>2 (3)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Mild acute rejection (grade IB) — no. (%)</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Moderate acute rejection (grade IIA) — no. (%)</td>
<td>2 (3)</td>
<td>3 (4)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Moderate acute rejection (grade IIB) — no. (%)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Subclinical rejection — no. (%)</td>
<td>7 (9)</td>
<td>14 (20)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Treated episode of subclinical rejection — no. (%)</td>
<td>6 (8)</td>
<td>11 (13)</td>
<td>5 (7)</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval.

Efalizumab Humanized anti CD-11a

- Humanized monoclonal against the alpha chain of the LFA-1 molecule
- LFA-1 is a classic adhesion molecule
- Member of the heterodimeric B2 integrin family LFA-1
- plays a role in stabilizing the immune synapse of the TCR-MHC complex
- Participates in costimulation
Efalizumab Humanized anti CD-11a

- In phase III studies in moderate to-severe psoriasis efalizumab, administered by subcutaneous injection, was found to be safe, well tolerated and effective
- This was a Phase 1 / 2 study in renal transplant
  - 38 patients
  - Weekly sc administration
  - 3 cases of PTLPD
Rituximab: B-cell Depletion

- Genetically engineered chimeric murine/human monoclonal antibody
  - Variable light- and heavy-chain regions from murine anti-CD20 antibody IDEC-2B8
  - Human IgGk constant regions
- First monoclonal antibody to be approved by the FDA for treatment of cancer
Rituximab – only targets peripheral CD20 positive B cells
FK 778

- analogue of the active metabolite of leflunomide
ISA 247

• An isomeric cyclosporine A analog mixture may be a more potent immunosuppressive agent than cyclosporine and less nephrotoxic
• There is an ongoing phase IIIb study of ISA247 versus tacrolimus
AEB071

- AEB071 is an oral protein kinase C inhibitor that inhibits T cell activation
- Phase 2 clinical kidney transplant trials are ongoing.
CP690550

- JAK 3 inhibitor
- Currently in phase II study
## Examples of Current and Experimental Immunosuppressive Drug Protocols

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Protocol Elements</th>
<th>Postadaption Maintenance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional treatment</td>
<td>Protein Induction: Anti-CD25 antibody, polyclonal antihymocyte globulin, or none</td>
<td>Preadaptation Maintenance: Calcinurin inhibitor, mycophenolate mofetil, and prednisone</td>
<td>Postadaption Maintenance: Calcinurin inhibitor and mycophenolate mofetil; prednisone tapered</td>
</tr>
<tr>
<td>Conventional treatment with no steroids</td>
<td>Anti-CD25 antibody, polyclonal antihymocyte globulin</td>
<td>Calcinurin inhibitor and mycophenolate mofetil; prednisone only if needed</td>
<td>Calcinurin inhibitor and mycophenolate mofetil; prednisone tapered</td>
</tr>
<tr>
<td>Conventional treatment with depleting antibodies</td>
<td>Polyclonal antihymocyte globulin</td>
<td>Calcinurin inhibitor, mycophenolate mofetil, and prednisone</td>
<td>Calcinurin inhibitor and mycophenolate mofetil; prednisone tapered</td>
</tr>
<tr>
<td>Sirolimus with cyclosporine withdrawal</td>
<td>Anti-CD25 antibody, polyclonal antihymocyte globulin, or none</td>
<td>Cyclosporine, sirolimus, and prednisone</td>
<td>Sirolimus; prednisone tapered</td>
</tr>
<tr>
<td>Calcineurin inhibitor avoidance with maintenance sirolimus and mycophenolate mofetil</td>
<td>Anti-CD25 antibody, polyclonal antihymocyte globulin, or none</td>
<td>Sirolimus, mycophenolate mofetil, and prednisone</td>
<td>Sirolimus and mycophenolate mofetil; prednisone tapered</td>
</tr>
<tr>
<td>Calcineurin inhibitor withdrawal with mycophenolate mofetil maintenance</td>
<td>Anti-CD25 antibody, polyclonal antihymocyte globulin, or none</td>
<td>Calcineurin inhibitor, mycophenolate mofetil, and prednisone</td>
<td>Mycophenolate mofetil; prednisone tapered</td>
</tr>
<tr>
<td>Alemtuzumab induction</td>
<td>Alemtuzumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depletion with minimization of immunosuppressive drugs</td>
<td>Polyclonal antihymocyte globulin</td>
<td>Tacrolimus only if no rejection</td>
<td>Minimal tacrolimus if no rejection</td>
</tr>
<tr>
<td>Maintenance with CTLA-4-Ig and mycophenolate mofetil</td>
<td>Anti-CD25 antibody</td>
<td>CTLA-4-Ig, mycophenolate mofetil, and prednisone</td>
<td>CTLA-4-Ig, mycophenolate mofetil, and prednisone</td>
</tr>
</tbody>
</table>

* For most protocols, no data are available regarding the relative cost and cost-effectiveness of the treatment and long-term requirements for the administration of prednisone.
† CTLA-4-Ig denotes cytotoxic T-lymphocyte-associated antigen 4 tetramer combined with the Fc portion of immunoglobulin G.