Immunosuppressive Management: Case-Based Approach

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Renal Transplantation: Present Status

- Mortality rates approximately 1% at 1 year
- Short-term graft survival: 95% at 1 year
- Acute rejection rates: 10-15%
- Can optimize combination regimens for individual patient comorbidities
- Long-term graft survival still suboptimal due to Ab-mediated rejection/CNI toxicity

Standard Protocols (2014)

**Induction**
AntiCD 25, Thymoglobulin, or Alemtuzumab

**Maintenance**
CNI (Cyclosporine, Tacrolimus)
Mycophenolate 1 gm bid or highest tolerated dose
Steroid tapered to 0.1 mg/kg/day or steroid free

Immunosuppressants in Clinical Use in 2014

**Maintenance**
- Prednisone
- Azathioprine
- Mycophenolate mofetil/EC
- Mycophenolate sodium
- Cyclosporine
- Tacrolimus
- Belatacept
- Sirolimus/Everolimus
**Belatacept**

- Co-stimulatory pathway blocker
- Must be given by IV infusion
- Compared to CSA – better renal function but more rejection (severe)
- Black box warning about PTLD

**Components of Most Maintenance Immunosuppressive Protocol**

<table>
<thead>
<tr>
<th>Class of Agent</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcineurin inhibitor</td>
<td>Cyclosporine, tacrolimus</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Dose and regimen</td>
</tr>
<tr>
<td>Antiproliferative</td>
<td>Azathioprine, MMF, mTOR inhibitors</td>
</tr>
</tbody>
</table>

**Decision Making on Immunosuppression**

- Assess immunologic risk of recipients
- Assess non-immunologic risk of recipients
- Evaluate quality of organ

**Immunologic High Risk**

- Retransplant
- HLA sensitization > 80%
- Ethnicity
- Age

**Determinants of Non-Immunologic Risk**

- Native kidney disease (recurrence)
- Hepatitis status (C, B)
- BMI
- Diabetes
- Cardiovascular disease
- Skeletal disease
Determinants of Quality of Organ

- Is this an ECD kidney i.e., age of donor?
- Risk of DGF i.e., cold ischemic time/pump time
- Reduced nephron mass i.e., size differential

### Expanded Criteria Donors (ECD)

- Expanded criteria donors (ECD) defined by RR>1.7 at 5 years
- Offers of OMM ECD limited to ECD recipient list
- Organ Center has 2 hours to place OMM ECD
- OPO has 6 hours after cross-clamp to identify local recipients, then must offer regionally and nationally
- Informed consent expected

### Relationship Between EPTS and Age

<table>
<thead>
<tr>
<th>Age</th>
<th>% on WL</th>
<th>Top 20% EPTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-25</td>
<td>2.8</td>
<td>96.7%</td>
</tr>
<tr>
<td>26-35</td>
<td>8.4</td>
<td>80.6%</td>
</tr>
<tr>
<td>36-45</td>
<td>16.3</td>
<td>43.8%</td>
</tr>
<tr>
<td>46-55</td>
<td>25.4</td>
<td>10.1%</td>
</tr>
<tr>
<td>56-65</td>
<td>29.8</td>
<td>0%</td>
</tr>
<tr>
<td>66-75</td>
<td>14.9</td>
<td>0%</td>
</tr>
<tr>
<td>76+</td>
<td>1.5</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Kidney Donor Profile Index (KDPI)

- Donor age
- Height
- Weight
- Ethnicity
- History of Hypertension
- History of Diabetes
- Cause of Death
- Serum Creatinine
- HCV Status
- DCD Status

### Graft Survival vs KDPI

5Y Graft Survival vs KDPI
Case

You have a 65-year old Caucasian male with end-stage renal disease due to hypertensive nephrosclerosis with stage 5 CKD. He has comorbid type 2 diabetes, moderate obesity, hyperlipidemia, although his coronary angiogram has revealed no high-grade stenotic lesions. He has been cleared for the transplant program in your area. He has several potential living donors and is also willing to be placed on the deceased donor waiting list. The best choice of a donor for him would be
Case
A. Deceased donor with KDPI of 90
B. A living donor from his 69-year old spouse
C. A standard criteria deceased donor
D. A 21-year old grandson
E. Continue on dialysis without transplantation because of the risk of the transplant procedure and its complications

Induction Agents

Polyclonal Antibodies
- Rabbit anti-thymocyte globulin (Thymoglobulin®)
- ATGAM® horse gammaglobulin to human thymocytes

Humanized Antibodies to IL-2 Receptors – CD25
- Basiliximab (Simulect®)
- Alemtuzumab (Campath) Humanized Anti-CD52 Pan Lymphocytic (B+ T cells) Monoclonal

Depleting Induction Agents

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Thymoglobulin®</th>
<th>Campath®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>Polyclonal Rabbit</td>
<td>Humanized Murine</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Central</td>
<td>Peripheral</td>
</tr>
<tr>
<td>“First” Dose Effects</td>
<td>1+</td>
<td>3+</td>
</tr>
<tr>
<td>Efficacy in Rejection</td>
<td>3+</td>
<td>3+</td>
</tr>
<tr>
<td>Infections</td>
<td>2+</td>
<td>3+</td>
</tr>
</tbody>
</table>

Pharmacologic Considerations of Basiliximab

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basiliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant technology</td>
<td>Chimerized</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Block IL-2Rα</td>
</tr>
<tr>
<td>Saturation concentration</td>
<td>0.1 to 0.4 µg/mL</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>0.4% anti-idiotype, 1.4% anti-isotype</td>
</tr>
<tr>
<td>Duration of IL-2 blockade</td>
<td>30 to 45 days</td>
</tr>
<tr>
<td>Half-life</td>
<td>7.2 ± 3.2 days</td>
</tr>
<tr>
<td>Dosing</td>
<td>IV infusion of IV bolus 20 mg-dose (2 doses on days 0 and 4)</td>
</tr>
</tbody>
</table>

Antibody Side Effects

Depleting Agents
- Cytokine release: Fever, cytopenias, flu-like symptoms; Rare – “capillary leak syndrome” +/- renal dysfunction
- Serum sickness
- Predisposition to infection: Viral (ie. CMV)
- Predisposition to malignancy, PTLD, EBV activation

Immune Modulators
- Virtually no side effects

Case
A 45-year old African American male is anticipating his second kidney transplant. His original renal disease was hypertensive nephrosclerosis. He lost his first graft after 5 years of function. There was no obvious acute rejection and his original allograft is still in place. He is now anticipating a live donor transplant from a friend. His tissue typing shows a 1A, 2B and 2DR mismatch. He is 50% sensitized versus the panel. His standard cross match against this particular donor is negative. You are asked to select an immunosuppressive regimen for this patient.

Case
A 45-year old African American male is anticipating his second kidney transplant. His original renal disease was hypertensive nephrosclerosis. He lost his first graft after 5 years of function. There was no obvious acute rejection and his original allograft is still in place. He is now anticipating a live donor transplant from a friend. His tissue typing shows a 1A, 2B and 2DR mismatch. He is 50% sensitized versus the panel. His standard cross match against this particular donor is negative. You are asked to select an immunosuppressive regimen for this patient.
Case
A. Thymoglobulin induction followed by tacrolimus, mycophenolate mofetil and prednisone
B. Basiliximab induction followed by tacrolimus, MMF and prednisone
C. Alemtuzumab induction followed by tacrolimus monotherapy and no corticosteroids
D. No induction with cyclosporine, mycophenolate mofetil and prednisone maintenance therapy
E. Plasma exchange plus IVIG pretransplant followed by thymoglobulin induction, tacrolimus, mycophenolate mofetil and prednisone

Alemtuzumab Induction in Renal Transplantation

Calcineurin Inhibitors
- Cyclosporine or tacrolimus
- Chemically unrelated
- Complex with intracellular binding protein blocks calcineurin’s ability to phosphorylate nuclear transcription factors.

Monitoring Calcineurin and mTOR Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Neoral/Generics</th>
<th>Tacrolimus/Generics</th>
<th>mTOR Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C₀ – does not predict AUC</td>
<td>C₀ – sufficient for monitoring</td>
<td>Timing does not matter for sirolimus but trough levels for everolimus</td>
</tr>
<tr>
<td></td>
<td>C₂ – better correlation with AUC but can be misleading</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Side Effects of CNI
- Nephrotoxicity
- Hypertension (CSA > Tacro)
- Post-transplant diabetes (Tacro > CSA)
- Neurological (Tacro)
- Hirsuitism (CSA)/Alopecia (Tacro)
- Hyperlipidemia (CSA > Tacro)
**CNI Nephrotoxicity**

\[ \downarrow \text{Nitric oxide} \quad \text{Catecholamines} \]

\[ \text{Endothelin} \quad \text{RENAL HEMODYNAMICS} \quad \text{Angiotensin} \]

\[ \uparrow \text{Thromboxane/\downarrow Vasodilator prostaglandins} \]

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**Side Effects of mTOR Inhibitors**

- Acne/Rash
- Mouth ulcers
- Hyperlipidemia
- Anemia, thrombocytopenia
- Swelling – proteinuria (rare)
- Pneumonitis (rare)

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**Hemodynamic Effects of Tacrolimus vs. CSA in Normals**

*Klein et al. 2002*

<table>
<thead>
<tr>
<th></th>
<th>GFR</th>
<th>ERPF</th>
<th>MABP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>2 Weeks</td>
<td>Baseline</td>
</tr>
<tr>
<td>CSA (100-200)</td>
<td>99</td>
<td>85</td>
<td>597</td>
</tr>
<tr>
<td>Tacrol (5-15)</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
</tr>
</tbody>
</table>

8 patients crossover design

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**Is There a Difference Between Cyclosporine and Tacrolimus?**

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Ruggenenti et al: CsA-induced Renal Hypoperfusion

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Renal Function Calculated GFR at Month 12 (Cockcroft-Gault)

<table>
<thead>
<tr>
<th>ITT</th>
<th>GFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Median</td>
</tr>
<tr>
<td>Normal-dose CsA</td>
<td>390</td>
</tr>
<tr>
<td>Low-dose CsA</td>
<td>399</td>
</tr>
<tr>
<td>Low-dose TAC</td>
<td>401</td>
</tr>
<tr>
<td>Low-dose SRL</td>
<td>399</td>
</tr>
</tbody>
</table>


Cumulative Probability of Biopsy-Proven Acute Rejection (Panel A) and Allograft Survival (Panel B), According to Study Group

SYMPHONY: 12-month Graft Survival, Patient Survival and Biopsy Proven Acute Rejection Rates

Tacrolimus: Practical Considerations

- GI/hematologic effects underestimated
- Dose 0.1 mg/kg – 0.15 mg/kg
- Therapeutic range (trough) 5-8 ≠ 10-15 ng/ml
- Biologic effects (tremor, paresthesias alopecia) marker for adequate dose independent of level

Metabolic Interactions That Decrease CNI Levels

- Antituberculosis drugs
  - Rifampin
  - Rifabutin
  - Isoniazid
- Anticonvulsants
  - Barbiturates
  - Phenytoin
  - Carbamazepine
- Herbal preparations
  - St John’s wort

Metabolic Interactions that Increase CNI Levels

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Macrolides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca Channel Blockers</td>
<td>Non-dihydropyridines</td>
</tr>
<tr>
<td>mTOR Inhibitors</td>
<td>Sirolimus, Everolimus</td>
</tr>
<tr>
<td>Antifungals</td>
<td>Ketoconazole, Fluconazole</td>
</tr>
</tbody>
</table>
Enterohepatic Circulation

MMF: Practical Considerations

- More than 2 gms per day usually not tolerated
- Many centers use 500-750 mg BID
- Hematologic effects common
- Myfortic\textsuperscript{®} 720 mg = 1 gm CellCept\textsuperscript{®}

Myfortic\textsuperscript{®}

- Enteric coated MMF – Na salt of MPA
- “Presumed” less GI toxicity
- Similar efficacy with CellCept\textsuperscript{®}

Generic Prescribing

- “Bioequivalence” defined in normal volunteers (n=30)
- Few studies in complex transplant recipients
- Drug class substitutions by non-MDs common
- Pharmacists often do not appreciate kinetic differences between drugs in a single class
- Who gets the savings?

Generics in Transplant 2013

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imuran\textsuperscript{®}</td>
<td>Azathioprine</td>
</tr>
<tr>
<td>Neoral\textsuperscript{®}</td>
<td>At least 3 generics</td>
</tr>
<tr>
<td>Prograf\textsuperscript{®}</td>
<td>2 generics</td>
</tr>
<tr>
<td>CellCept\textsuperscript{®}</td>
<td>6 new generics</td>
</tr>
<tr>
<td>Myfortic\textsuperscript{®}</td>
<td>No generic</td>
</tr>
<tr>
<td>Sandimmune\textsuperscript{®}</td>
<td>Multiple generics for cyclosporine non-modified</td>
</tr>
<tr>
<td>Rapamune\textsuperscript{®}</td>
<td>No generic</td>
</tr>
<tr>
<td>Zortress\textsuperscript{®}</td>
<td>No generic</td>
</tr>
<tr>
<td>Deltasone\textsuperscript{®}</td>
<td>Multiple generics</td>
</tr>
</tbody>
</table>

*Not bioequivalent
Case
A 46-year old Asian female received a living related donor transplant from her haploidentical sister 6 months ago. She presents to you with fever, increasing allograft discomfort, elevation of blood pressure and slight peripheral edema. Her maintenance immunosuppressive regimen is prednisone 5 mg daily, cyclosporine microemulsion 100 mg bid, and mycophenolate mofetil 1 gm bid. She had received basiliximab induction therapy. Her last cyclosporine blood level 5 days ago was 100 nanograms/mL. Urinalysis shows 1+ protein, specific gravity of 1.015, 4-10 red cells and 6-10 white cells per high power field. Bacteria are not present. Her donor was CMV positive and she is CMV negative. She has received six months of valganciclovir prophylaxis. An ultrasound of her transplant reveals increased resistive indices but no evidence of hydronephrosis. Serum creatinine at the time of her cyclosporine blood level was 1.1 mg/dL and today's value is 1.4 mg/dL. The most likely diagnosis in this patient is:

A. Acute cellular allograft rejection
B. Primary CMV infection with renal involvement
C. Cyclosporine nephrotoxicity
D. Allograft pyelonephritis
E. Acute interstitial nephritis due to valganciclovir

Acute Cellular Rejection
- Most common cause of renal dysfunction 1-3 months post-transplant
- Diagnosis by biopsy – “tubulitis”
- Can be subclinical ie. surveillance biopsy
- Rx – corticosteroid pulse followed by biologic if resistant

Case
You are following a 36-year old Caucasian man with end-stage renal disease secondary to chronic IgA nephropathy. He received a renal transplant from his father six years ago. He is maintained on tacrolimus, mycophenolate mofetil, and low dose prednisone therapy. Early after transplant he had an acute rejection that was characterized by peritubular capillary neuropilic inflammation and C4D positivity.

On a routine visit in your office he is found to have an increased urinary protein/creatinine ratio and a rise in serum creatinine from a baseline of 1.3 mg/dL to 1.7 mg/dL. Blood pressure has gradually become more difficult to control and he is on metoprolol 50 mg bid and amlodipine 10 mg daily with marginal control. In addition to the proteinuria the urinalysis shows 0-3 red blood cells and 2-3 white blood cells per high power field. There are no casts present. Hemogram reveals a hemoglobin of 10.5 grams, white blood count of 4600 and a platelet count of 120,000. His last tacrolimus was 6 nanograms/mL. Ultrasound reveals no evidence of obstructive uropathy. Urine surveillance for polyoma virus shows 10⁴ log copies of BK virus. Serum BK PCR is negative. A renal biopsy is performed. You would most likely observe:

A. Interstitial nephritis with large viral inclusion bodies in proximal tubule cells
B. Arteriolar hylanosis suggestive of calcineurin inhibitor nephrotoxicity
C. Recurrence of IgA nephropathy in the transplanted kidney
D. Chronic tubular interstitial fibrosis plus glomerular lesions suggesting splitting and reduplication of glomerular basement membrane
E. Acute interstitial nephritis with extensive tubulitis

Antibody Mediated Rejection
- C4D deposition
- Donor specific antibodies
- Glomerular changes similar to MPGN “allograft glomerulopathy”
- Peritubular capillaritis-interstitial hemorrhage
- Rx – Pheresis, IVIG, Rituximab, ?Bortezemib
?Eculizimab. Success related to time post-transplant
Chronic Allograft Loss

- Slow deterioration due to humoral immunologic processes
- Non-immunologic factors including patient death, donor changes
- Calcineurin-inhibitor nephrotoxicity
- Recurrent or de novo nephropathy

Case

A 64-year old Caucasian male received a deceased donor transplant six months ago. Kidney function has been excellent with baseline serum creatinines of 1.1-1.2 mg/dl. At the past several clinic visits he is noted to have 5-10 red blood cells per high power field. An ultrasound of his renal transplant reveals a very mild hydronephrosis. His urine to protein creatinine ratio is 0.1, and his serum creatinine on today’s visit is 1.4 mg/dl. Immunosuppression since the time of transplant has been mycophenolate mofetil 1 gm BID, tacrolimus maintaining a blood level of 8-10 ng/ml, and prednisone 5 mg daily. A renal biopsy shows some interstitial inflammatory cells. C4D staining is negative. You would next...

Causes of Late Kidney Allograft Loss

- Chronic allograft nephropathy leading to graft failure in 50% of cases
- Death of a patient with a functioning graft in 50% of cases
- Other diagnoses in 10-20% of cases
  - Chronic allograft nephropathy in 30-40% of cases
  - True chronic rejection (immunologic injury)
  - IF/TA of mixed origin (e.g., nonspecific interstitial fibrosis and tubular atrophy)
  - Chronic toxic effects of calcineurin inhibitors
  - New diseases
  - Acute rejection

A. Insert an antegrade stent to bypass the ureteral obstruction to see if renal function improves
B. Treat the patient with high dose steroids for acute rejection
C. Perform an allograft biopsy
D. Cystoscope the patient looking for bladder tumors
E. Examine urinary PCR for BK virus
### Emerging CS Sparing Regimens

- Rapid withdrawal (< 7 days after transplantation)
- Complete elimination

### Advantages of Very Early Withdrawal or Complete Avoidance of Corticosteroids in Renal Transplantation

- Acute rejection may occur early and be readily diagnosed and treated
- The host’s immune response remains unmodified by the effect of chronic steroid therapy
  - No interference by steroids of tolerogenic pathway
  - Lack of steroid dependency
  - Prevention of heightened immune response after discontinuation of steroids
- Prevention of steroid side effects

### A Prospective, Randomized, Double-Blind, Placebo-Controlled Multicenter Trial Comparing Early (7 Day) Corticosteroid Cessation Versus Long-Term, Low-Dose Corticosteroid Therapy

**Woodle ES, Fitzsimmons W, First MR, Pirsch J, Shihab F, Gaber AO, Van Veldheisen P; Astellas Corticosteroid Withdrawal Study Group**


### Primary Endpoint of Death, Graft Loss, or Moderate/Severe Acute Rejection: Kaplan-Meier Analysis

<table>
<thead>
<tr>
<th>Years Posttransplant</th>
<th>Chronic low-dose corticosteroid therapy</th>
<th>Early corticosteroid withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability (%)</td>
<td>84.9%</td>
<td>83.3%</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.691</td>
<td></td>
</tr>
</tbody>
</table>

### Biopsy-Confirmed Acute Rejection

<table>
<thead>
<tr>
<th>Years Posttransplant</th>
<th>Chronic low-dose corticosteroid therapy</th>
<th>Early corticosteroid withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability (%)</td>
<td>27.3%</td>
<td>17.0%</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

### Chronic Allograft Nephropathy at 5 Years

<table>
<thead>
<tr>
<th>Biopsy-confirmed CAN</th>
<th>CCS N=195</th>
<th>CSWD N=191</th>
<th><strong>P</strong> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy-confirmed CAN</td>
<td>8 (4.1%)</td>
<td>19 (9.9%)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

CAN=chronic allograft nephropathy; CCS=chronic low-dose corticosteroid therapy; CSWD=early corticosteroid withdrawal
**Summary**

- Very early corticosteroid appears to be safe in low immunologic risk patients
- Longer-term follow-up is still required

**Drugs in Pregnant Transplant Patients**

- Prednisone – safe, ↑ perinatal dose for labor ‘stress’
- Azathioprine – safe
- Cyclosporine/tacrolimus – same blood concentration in fetus as mother, ? IGR or small for age babies
- Mycophenolate/sirolimus, everolimus – limited data
- BP drugs: methyldopa, hydralazine, labetolol

**Bortezomib**

- Approved for myeloma
- Acts early in B cell pathway (proteosome inhibitor)
- Given IV
- Use for humoral rejection and desensitization “off label”
- Neurotoxicity and hematologic effects

**Eculizimab**

- Humanized monoclonal antibody against C5 protein
- Prevents C5b-C9 complex
- Approved for PNH, atypical HUS
- Off label – desensitization, AMR
- EXPENSIVE!

**Key Points**

- Kidney transplant is treatment of choice for ESRD
- Standard regimen: Triple drug – CNI, MPA, steroid
- Steroid withdrawal safe in short term
- Antibody mediated processes major cause of CAN
- Drug interactions are frequent and clinically important
Immunosuppressive Drugs: Mechanisms of Action and Issues for Use

Douglas J. Norman, MD
Professor of Medicine
Oregon Health & Science University

The Phases of Immunosuppression

ARS: Which drugs are blockers of signal 3 of the T cell activation cascade?

- 1. Cyclosporine, tacrolimus, everolimus
- 2. MMF, Azathioprine, leflunamide
- 3. Belatacept, MMF, sirolimus
- 4. Basiliximab, tacrolimus, OKT3
- 5. OKT3, cyclosporine, tacrolimus

Antilymphocyte Antibodies

- Polyclonal
  - Atgam (equine)
  - Thymoglobulin (rabbit)
- Monoclonal
  - Murine (100% mouse)
    - OKT3 (anti CD3)
  - Human/Murine
    - Chimeric (70% human)
      - Basiliximab (anti IL2R)
    - Humanized (90% human)
      - Alemtuzumab (anti CD52)
**Mechanisms of Action of Antilymphocyte Antibodies**

- **Cell Depletion (most effective)**
  - opsonization / phagocytosis
  - complement mediated lysis
  - apoptosis
  - antibody dependent cell mediated cytotoxicity
- **Blocking function of T cells**
  - removes functional molecules from cell surface
  - occupies functional molecule to prevent ligand binding

**ARS: What is a true statement about antilymphocyte antibodies?**

- 1. Chimeric monoclonal antibodies are mostly murine
- 2. Humanized monoclonal antibodies are 50% human
- 3. Thymoglobulin and basiliximab are polyclonal antibodies
- 4. Alemtuzumab is a 90% human monoclonal antibody
- 5. Atgam is a rabbit polyclonal antibody

**Important Additional Issues Regarding Immunosuppression**

- Never use azathioprine with allopurinol
- MMF may have selective lymphocyte activity because it acts through the de novo pathway of purine synthesis
- OKT3, Thymoglobulin and Atgam can cause a cytokine release syndrome that can be significant

**Key Board Review Points**

- T cell signal 1 blockers have been the most important drugs used in kidney transplantation
- T cell signal 3 blockers have mostly been used as adjuvant treatments
- Antilymphocyte antibodies block the immune response mostly by depleting lymphocytes but some inactivate T cells by blocking a functional molecule on the cell surface
- Azathioprine should never be used with allopurinol (xanthine oxidase inhibitor)

**Initial Immunosuppression**

- Pretransplant
- Immune Desensitization
- Induction Therapy
- Posttransplant
- Acute Post-Transplant Immunosuppression
- Pre-Transplant Immunosuppression
**Immune Desensitization**

- Plasmapheresis
- IVIG
- Rituximab
- Bortezomib

**ARS: Why is strong immunosuppression used initially following kidney transplantation?**

1. The indirect pathway of T cell activation is prominent
2. The direct pathway of T cell activation is prominent
3. Infections are uncommon during the first 3 months following transplantation
4. Delayed graft function can be prevented using strong immunosuppression
5. Living donor kidneys are more immunogenetic than deceased donor kidneys

**Direct Allorecognition**

**Induction Immunosuppression**

- Antilymphocyte antibody
- Methylprednisolone, 500mg IV on day 0
- Antiproliferative drug (sirolimus should be avoided because of wound healing problems)

**Odds Ratios For Allograft Loss when ATG or OKT3 used for Induction**

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michael</td>
<td>0.63 (0.18, 2.2)</td>
</tr>
<tr>
<td>Beltsky</td>
<td>1.57 (0.56, 4.41)</td>
</tr>
<tr>
<td>Banhegyi</td>
<td>0.71 (0.19, 2.65)</td>
</tr>
<tr>
<td>Abramowicz</td>
<td>0.50 (0.19, 1.33)</td>
</tr>
<tr>
<td>Norman</td>
<td>0.56 (0.28, 1.12)</td>
</tr>
<tr>
<td>Slakey</td>
<td>0.52 (0.19, 1.42)</td>
</tr>
<tr>
<td>SMSG*</td>
<td>0.67 (0.20, 2.33)</td>
</tr>
<tr>
<td>OVERALL</td>
<td>0.66 (0.45, 0.96)</td>
</tr>
</tbody>
</table>

*Spanish monoclonal antibody study group

**Meta-analysis of Randomized Trials Of Anti-IL2R* in Kidney Transplantation: 8 trials involving 1816 Patients**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Rejection</td>
<td>0.51 (0.42, 0.62)</td>
</tr>
<tr>
<td>Graft Loss</td>
<td>0.78 (0.58, 1.05)</td>
</tr>
<tr>
<td>Patient Mortality</td>
<td>0.75 (0.46, 1.22)</td>
</tr>
<tr>
<td>Infections</td>
<td>0.97 (0.77, 1.23)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>0.88 (0.43, 1.82)</td>
</tr>
</tbody>
</table>

*anti-tac, BT 563, basiliximab or daclizumab

Cockwell PJ, Ives N, Wheatley K et al. ATC 2002
Key Board Review Points

Induction Drugs and Protocols

- Strong immunosuppression must be used initially following kidney transplantation because the direct pathway of T cell activation is prominent.
- Most induction protocols are currently including an antilymphocyte antibody.
- Immune desensitization might be necessary prior to kidney transplantation if donor specific antibodies are present.
- The use of antilymphocyte antibodies increases the risk of infection and lymphoproliferative disease.

Treatment of Rejection

When Rejections Occur

- Hyperacute Rejection
- Antibody Mediated Rejection
- Acute Recognition of Chronic Rejection
- Early Acute Rejection
- Late Acute Rejection

Treatment of Cell Mediated Rejection

- Corticosteroids
- Anti lymphocyte antibodies
  - Thymoglobulin, OKT3
- Increase maintenance drugs
  - Signal 1 and signal 3 blockers
### Treatment of Antibody Mediated Rejection

- **B-cell inactivation**
  - Thymoglobulin, Rituximab, IVIG, Bortezomib
- **Alloantibody removal**
  - Plasmapheresis
  - Alloantibody neutralization/modulation
  - IVIG

### Rituximab (Rituxan®)

- Binds to CD20 on naïve and resting memory B cells
- Does not bind to plasma cells
- No cytokine release syndrome
- Used in immune desensitization protocols for high PRA

### Intravenous Immunoglobulin (IVIG)

- Down-regulates antibody production by plasma cells
- Induces apoptosis of B cells
- Effective for treatment of acute humoral rejection and immune desensitization protocols

### Bortezomib (Velcade®)

- Protease inhibitor
- Used to treat multiple myeloma
- Purpose is to reduce antibody production by plasma cells

### Plasmapheresis

- Removes circulating antibodies
- Used as temporizing measure while anti-B cell/plasma cell therapies are started
- Effective for treatment of acute humoral rejection and immune desensitization protocols

### ARS: What are possible treatments for cell mediated rejection?

1. Corticosteroids, rituximab, plasmapheresis
2. Corticosteroids, thymoglobulin, IVIG
3. Corticosteroids, thymoglobulin, bortezomib
4. Corticosteroids, thymoglobulin, increase signal 1 blockers
Key Board Review Points
Treatment of rejection

• Mild or moderate cell mediated rejection should be treated with corticosteroids first
• Severe cell mediated rejection should be treated with an antilymphocyte antibody first ± corticosteroids
• Early antibody mediated rejection can be treated successfully
• Treatment of chronic rejection, acutely recognized, is usually unsuccessful

Key Update Points
Treatment of rejection

• Some kidney transplant programs use surveillance biopsies at one or more time points in the first two years after transplant
• Surveillance biopsies clearly demonstrate that rejection can occur in the absence of clinical manifestations (stable, normal creatinine)

THE END
Friday, August 6

Post-Transplant Non-Infectious Complications

Donald E. Hricik, MD

9:30 a.m. - 11:00 a.m.
Noninfectious Complications of Kidney Transplantation

Donald E. Hricik, M.D.
Professor of Medicine and Chief, Division of Nephrology and Hypertension
Director, Transplant Institute
University Hospitals Case Medical Center

Overview: Complications of Transplantation

- Early Complications
  - Surgical complications

- Later Complications
  - Cardiovascular disease
    - Hypertension
    - Hyperlipidemia
    - Diabetes mellitus
    - Anemia/erythrocytosis
    - Chronic allograft dysfunction
    - Malignancy
    - Bone disease
      - Managing the failed transplant

Surgical Complications – Kidney Transplantation

- Wound infections
- Fluid Collections – Vascular
  - Seromas
  - Hematomas
  - Mycotic aneurysm (rare; > 50% mortality)
  - Renal rupture (acute rejection; rare)
  - Management: variable
    - Lymphocele (5-15% of cases; more common with TOR inhibitors)
      - Management: conservative when non-obstructing, or:
        - Percutaneous drainage
        - 30% require surgical repair

- Fluid Collections – Urologic
  - Urine Leaks (1-3% of cases)
    - Diagnosis: Creatinine ratio – fluid collection: serum; nuclear scans
    - Management:
      - Prolonged bladder drainage +/- ureteral stenting
      - Surgical repair:
        - Repeat implantation into bladder
        - Ureter-ureter reconstruction

- Decreased diuresis – urologic
  - Compression of the ureter
  - Urine leak
  - Obstruction of the urinary tract at any level
    - Ureteral blood clot/tissue/stone/kink
    - Bladder outlet obstruction
      - (Later cases of obstructive uropathy more often related to ischemic strictures or BK polyoma infection)
  - Decreased diuresis – vascular
    - Arterial or venous thrombosis 1-2% of cases
      - Diagnosis: Doppler ultrasound (no flow)
      - Management – immediate surgical exploration

Surgical Complications – Kidney Transplantation, continued

Cadaveric Renal Allograft Survival

Adapted from Stewart F, Organ Transplantation, 1999
Long term allograft survival: Progress or time to rethink strategies?

Late allograft loss (>1 yr after transplantation)
- 40% Death with functioning graft
- 50% Cardiovascular disease
  - Drug toxicity
  - New diseases
  - Recurrent diseases
  - Acute rejection

50% Chronic renal allograft dysfunction
10% - 20% Chronic rejection
30% - 40% Non-specific fibrosis, tubular atrophy
50% Other diagnoses

Causes of Late Kidney Allograft Loss

- Chronic renal allograft dysfunction: 50%
- Death with functioning graft: 50%
- Cardiovascular disease: 10%–20%
- Other diagnoses: 50%

Interim Summary
• Board Review Points
  - Incidence of acute rejection in first posttransplant year < 20%
  - Improvement in rates of acute rejection not paralleled by improvements in long-term graft survival
  - Death with a functioning graft accounts for ~ 40% of late graft losses
• Update Points
  - Wound healing is impaired by and lymphoceles are more common with TOR inhibitors

Cardiovascular Mortality in Renal Transplant Recipients

- General: 0.28%
- Hemodialysis: 9.12%
- Peritoneal dialysis: 9.24%
- Renal transplant: 0.54%

Which of the following is the most common cause of mortality after kidney transplantation?
• A. Posttransplant lymphoproliferative disease
• B. Myocardial infarction
• C. Opportunistic infection
• D. Squamous cell carcinoma
**Aker S et al.**

Single-center retrospective study (N = 427)

Error bars represent 95% CI

---

CyA = cyclosporine; Tac = tacrolimus; SRL = sirolimus

+++ = severe; ++ = moderate; + = mild; – = opposite; ± = none; ? = unknown

---

**Tremor**

Hyperkalemia

Hyperlipidemia

Renal insufficiency

Hyperglycemia

Malignancy

Osteoporosis

Hirsutism

Gingival hyperplasia

Hypophosphatemia

Gingival hyperplasia

Hypertension

Hypophosphatemia

SBP values (mm Hg)

SBP = systolic blood pressure


---

**Association of Hypertension at 1 Year With Decreased Graft Survival**

SBP = systolic blood pressure


---

**Pathogenesis of Hypertension in Renal Transplant Recipients**

- Pre-existing essential hypertension
- General-population risk factors (obesity, alcohol, excessive salt intake)
- Renal dysfunction/rejection
- Renal-transplant artery stenosis
- Effects of native kidneys
- Hypertensive donor
- Immunosuppressive drugs
- Steroids; CNIs (CsA>FK)


Transplant Renal Artery Stenosis

- Prevalence 5-25%
- Highest rates between 3 months and 2 years
- Pathophysiology: Anastomotic strictures (more common after live donor transplantation), arterial kinks, rejection, proximal stenoses in the recipient’s aorto-iliac arterial tree
- Clinical presentation: Worsening hypertension, “creatinine creep”
- Diagnosis: Doppler US, MRA, gold standard is arteriography
- Treatment: PTA, surgery

Posttransplant Hypertension: Treatment

- All antihypertensive drugs work!
- No established algorithm, but consider:
  - Interactions between immunosuppressive meds and BP meds (diltiazem, verapamil increase CNI and TORi levels)
  - Side effects of BP meds
  - Cost and number of medications!
  - HTN is a side effect of IS medications

ACEIs and ARBs in Kidney Transplantation

- Hyperkalemia
- Antiproteinuric
- Renal Protection
- Acute Renal Failure (rare)
- Anemia

Kaplan-Meier estimates of patient survival

ACEIs/ARBs Do not Influence Graft or Patient Survival

Losartan vs Placebo in Kidney Transplant Recipients

- Prospective randomized double blind placebo controlled
- Randomization at 3 months to losartan (n=77) vs placebo (n=76)
- 5 year follow-up
- Composite endpoint of doubling of interstitial volume on serial biopsies or ESRD attributed to IFTA
- Results: No statistically significant benefit of losartan
Pathogenesis of Hyperlipidemia in Renal Transplant Recipients (prevalence of 60-90% depending on immunosuppressive regimen*)

- High prevalence of predisposing factors¹
  - Age
  - Diabetes
  - Obesity
  - Impaired renal function²
  - Renal insufficiency
  - Proteinuria
- Drugs³
  - Diuretics, beta-blockers
  - Immunosuppressive agents
  - Steroids, CNIs, TOR inhibitors


Characterization of Hyperlipidemia Associated With Sirolimus

- ↑ Total-C and TG (increase LDL, VLDL, and HDL)
- Mechanism: ↓ catabolism of apoB-100–containing lipoproteins¹
  - Dose dependent
  - Generally reversible upon cessation
  - Responsive to lipid-reducing agents
    - No clinically significant interaction with atorvastatin²


Cyclosporine vs Tacrolimus

Effect of Sirolimus on Aortic Atherosclerosis in ApoE-Deficient Mice

Interim Summary

- Board Review Points
  - Cardiovascular disease most common cause of death
  - ACEIs and ARBs have been associated with posttransplant anemia (and used to treat erythrocytosis)
  - Hyperlipidemia more common with CsA than with tacrolimus


*Fluvastatin 40-80 mg/day
Mean follow-up 5 years
Total cardiac events not reduced significantly

Mean total cholesterol level over time

- Baseline
- 1 Year
- 3 Years
- 5 Years

- Cyclosporine
- Tacrolimus

- Randomized, multicenter trial with traditional formulation of cyclosporine

- Control
- 8 mg/kg/d x 2 d


- ALERT Trial (n=2102)∗
- Cumulative incidence of cardiac death or Nonfatal definite MI - Core Study

- Proportion of patients with event (%)
- Years since randomization
  - Fluvastatin 40-80 mg/day
  - Mean follow-up 5 years
  - Total cardiac events not reduced significantly

- Update Points
  - Cardiovascular disease linked to renal impairment after transplantation
  - Incidence of cardiovascular events decrease after transplantation
  - TOR inhibitors may be anti-atherogenic
  - Has been difficult to prove any renoprotective effect of ACEIs or ARBs in kidney transplantation
Which of the following factors is most strongly associated with new onset of diabetes mellitus after kidney transplantation?

- A. Hepatitis C
- B. Obesity
- C. Advanced recipient age
- D. Use of tacrolimus
- E. Advanced donor recipient age

**Classification of Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Category</th>
<th>ADA 2004</th>
<th>WHO 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;100</td>
<td>&lt;110</td>
</tr>
<tr>
<td>Impaired Fasting Glucose</td>
<td>100-125</td>
<td>110-125</td>
</tr>
<tr>
<td>Impaired Glucose Tolerance</td>
<td>2h PPG 140-199</td>
<td>2h PPG 140-199</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>FPG ≥ 126 or 2h PPG &gt; 200</td>
<td>FPG ≥ 126 or 2h PPG &gt; 200</td>
</tr>
</tbody>
</table>

**Survival Free of Posttransplant Diabetes Based on Medicare Claims**

- 3 months (9.1%)
- 12 months (16%)
- 36 months (24%)


**Risk factors for the development of post-transplant hyperglycemia**

- Obese
- Older age
- Family Hx of DM
- Black/Hispanic
- Insulin resistance / low GFR
- Hepatitis C
- Hypermagnesemia; Statins
- APKD?

**PTDM: Independent Risk Factors**

<table>
<thead>
<tr>
<th>Clinical Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60</td>
<td>2.60</td>
</tr>
<tr>
<td>Age 49-59</td>
<td>1.90</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td>1.73</td>
</tr>
<tr>
<td>African American</td>
<td>1.68</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>1.35</td>
</tr>
<tr>
<td>Hepatitis C Antibodies</td>
<td>1.33</td>
</tr>
</tbody>
</table>

Kasiske et al. AJT 2003 3:178

**Tacrolimus is more diabetogenic than cyclosporine**

(Kasiske et al. AJT 3:178, 2003)
Cumulative incidence of cardiovascular events five years posttransplant in patients classified according to fasting glycemia at 1 year


Diabetes (pre or post-transplant) has a profound impact on recipient survival

Adapted from Cosio et al. K Int 2002:62:1440  Follow up months

Nonpharmacologic Therapy (Weight Loss; Exercise)

Oral Hypoglycemic Agent Monotherapy

? Manipulation of Immunosuppression

Combination of Oral Agents

Insulin Plus Oral Agents

Insulin Monotherapy

STEPWISE APPROACH TO TREATMENT OF NODAT

Which of the following factors is most strongly associated with posttransplant anemia?

- A. Impaired allograft function
- B. Use of TOR inhibitors
- C. Use of ACE inhibitors or ARBs
- D. Number of acute rejection episodes

Changes in Hematocrit after Kidney Transplantation


Hematocrit levels at different levels of kidney function


- Impaired renal function
- Use of ACEIs or ARBs (after excluding ~ 5-10% of patients with post-transplantation erythrocytosis)
- Use of mycophenolate mofetil or azathioprine (no patients on sirolimus included in analysis)

Sirolimus and Post-Transplant Anemia

- SRL inhibits erythropoiesis at level of EPO receptor
- Binding of EPO to receptor activates phosphorylating enzymes including PI 3-kinase which is responsible for controlling cell survival and cell cycle progression
- SRL inhibits kinase p70S6k, a downstream enzyme

Freedom from Cardiovascular Events in Type 1 Diabetics based on Anemia in the First 6 Months (Djamali A, et al: 2003; 76:816)

- Cardiovascular event = CV death, MI, or hospitalization for CHF or angina

Renal function at inclusion

Evolution of serum Hb level during the study

- Blood transfusion 1 (1.6 %) in A, and 5 (8.1 %) in B

Interim Summary

- Board Review Points
  - Risk Factors for NODAT: Age, BMI, ethnicity, hepatitis C
  - Tacrolimus more diabetogenic than cyclosporine
  - Anemia related to antiproliferative immunosuppressants – MMF, AZA, and especially sirolimus

- Update Points
  - Sirolimus can be diabetogenic
  - NODAT associated with increased risk of cardiovascular disease and death
  - Anemia linked to cardiovascular death and decreased patient survival after transplantation
  - CAPRIT study suggests correction of anemia improves allograft function
Differential Diagnosis of Late Renal Allograft Dysfunction

- ↓ Immunosuppression
  - Calcineurin inhibitor toxicity
  - BK virus nephropathy

- ↑ Immunosuppression
  - Late acute rejection
  - Chronic humoral rejection
  - Recurrence of original renal disease
  - De-novo renal disease

- Other Intervention
  - Medication effect (NSAID)
  - Renal artery stenosis
  - Obstructive uropathy
  - Interstitial nephritis
  - Pre-renal (CHF, cirrhosis)

Recurrence of Primary Renal Disease in the Transplanted Kidney

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency of Recurrence (%)</th>
<th>Graft Loss Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal glomerulosclerosis</td>
<td>23–43</td>
<td>11–50</td>
</tr>
<tr>
<td>Membranoproliferative type I</td>
<td>20–40</td>
<td>33</td>
</tr>
<tr>
<td>Membranoproliferative type II</td>
<td>88–100</td>
<td>50</td>
</tr>
<tr>
<td>Membranous (recurrence)</td>
<td>10</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Membranous (de novo)</td>
<td>4–9</td>
<td></td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>8–50</td>
<td>1</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>75–88</td>
<td>20–40</td>
</tr>
<tr>
<td>Anti-GBM nephritis</td>
<td>12</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Hemolytic-uremic syndrome</td>
<td>13–25</td>
<td>40–50</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>&lt; 1</td>
<td>None</td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
<td>30–45</td>
<td>10–25</td>
</tr>
</tbody>
</table>

Renal Toxicity of Calcineurin Inhibitor

- Acute toxicity
- Chronic toxicity
- Occurs in native kidneys

Inflammation and Graft Survival

- Retrospective analysis of long-term outcome of kidney grafts related to biopsy at 1 yr (N = 292)
- 6 patients with inflammation and no fibrosis
- Pathologic diagnoses
  - Acute rejection (n = 3)
  - BK nephropathy (n = 1)
  - Pyelonephritis (n = 1)
  - Nonspecific findings (n = 1)
- In patients with fibrosis, level of inflammation associated with worse outcome


HLA Antibodies Predict Kidney Graft Failure

- Post-Tx Ab-
- Post-Tx Ab+
- Total

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Ab+ PreTx</th>
<th>Ab- PreTx</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Tx Ab-</td>
<td>6.6%*</td>
<td>3.5%</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Post-Tx Ab+</td>
<td>2.1%</td>
<td>3.9%</td>
<td>6%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Total</td>
<td>3.8%</td>
<td>3%</td>
<td>3.8%</td>
<td>6.6%</td>
</tr>
</tbody>
</table>

*p<0.007 vs. Ab-; †p<0.05 vs. Ab-; ‡p<0.0003 vs. Ab-.


Prediction of graft survival by molecularly diagnosed ABMR

- Training set 112 patients
- Validation set 154 patients

CAN: Treatment Options

- Medical Renal Therapy
  - ACE-I or ARB treatment
  - Control blood pressure
  - Glycemic control

- Alter immunosuppression
  - Add Antiproliferative Agents
  - Decrease Calcineurin Inhibitors (but may be dangerous with chronic humoral rejection)
  - Change to TOR Inhibitors
Chronic Humoral Rejection (Transplant Glomerulopathy): Treatment

- Treatment of accompanying cellular rejection
- ? Plasmapheresis
- ? IVIg
- ? Proteasome Inhibitors (eg Bortezemib)
- ? Complement Inhibitors (eg Ecalizumab)

Renal Function Improves With Sirolimus After Early Cyclosporine Withdrawal

CONVERT Trial - Treatment Regimens

SRL Conversion vs CNI Continuation

Pre-Randomization: Corticosteroids
- MMF or AZA
- CsA or Tacrolimus

Randomization: 2:1

(n=555) (n=275)

SRL Conversion
- Day 1: Stop CNI; SRL, 12-20 mg x1
- Day 2: SRL 4-8 mg/day
- Days 5-7: Adjust to 8-20 ng/mL
- MMF or AZA: Continue or stop
- Continue corticosteroids

CNI Continuation
- Continue CsA or tacrolimus (can switch CsA to tacro)
- MMF or AZA: Continue or stop
- Continue corticosteroids

Routine follow-up per protocol

Summary

At 1 Year, conversion to SRL was associated with:

- Significantly higher GFR in patients remaining on therapy with baseline GFR >40 mL/min
- Greater improvement in GFR in patients with less proteinuria at baseline
- Significantly fewer malignancies
- No increase in acute rejection
- Excellent patient and graft survival
- Adverse events consistent with known SRL safety profile.

Interim Summary

- Board Review Points
  - "Chronic allograft nephropathy" is not a single histologic entity
  - IFTA and Transplant Glomerulopathy can appear together or alone
  - Conversion from CNIs to TOR inhibitors is not very successful in patients with even moderate renal impairment or preexisting proteinuria

- Update Points
  - In the absence of associated inflammation, fibrosis alone is not a strong harbinger of graft loss
  - The late development of donor specific antibodies is now recognized as an important cause of graft loss; treatment options are suboptimal

Compared to the general population, which malignancy occurs after transplantation with the highest relative risk?

- A. Lymphoma
- B. Nonmelanoma skin cancer
- C. Kaposi’s sarcoma
- D. Lung cancer
Cancers that Are Increased Compared to the General Population

- **Much higher:**
  - Skin*
  - Kaposi's*
  - Vulvovaginal*
  - Lymphoma*
  - Kidney

- **Higher:**
  - Uterine cervix*
  - Esophagus
  - Liver*

- **Not different:**
  - Breast
  - Prostate
  - Testicular
  - Ovarian
  - Lung
  - Colon

* Viral etiology known or suspected in most cases

Risk factors for SCC/BCC

- Age at transplantation: 12x increase if >55y versus <34 y
- Duration of transplantation: 40-60% by 20y (70-82% in Australia)
- Skin phototypes III: eye and hair colour, susceptibility to sunburn
- UVR exposure - acute (sunburn <18y) and chronic
- History of skin cancer
- Organ transplanted: cardiac > renal > liver
- Presence of AKs and viral warts or 'keratotic' lesions

Sirolimus in non-melanoma skin cancer

Baseline 12 months later


Sirolimus for Kaposi’s Sarcoma

- 15 kidney transplant recipients
- Biopsy-proven Kaposi’s Sarcoma
- Treatment:
  - CsA was discontinued
  - Sirolimus was begun
- Outcome:
  - No lesions at 3 months
  - Confirmed by biopsy


Post-Transplant Lymphoproliferative Disease (PTLD)

- Lymphoma occurring post-transplant related to immunosuppression
  - EBV mediated (80% of cases) polyclonal, monoclonal
  - Non-EBV mediated
- Most within 2 years post-transplant
  - Increased risk with high immunosuppression
- Lesions within transplanted organ are common
- Treatment: lower immunosuppression, anti-CD20 therapy (rituximab), chemotherapy

Posttransplant Bone Disease:

1) Avascular necrosis
2) Osteopenia
Compared to osteopenic patients in the general population, osteopenic transplant recipients demonstrate:

- A. Better response to bisphosphonates
- B. More appendicular fractures than spinal fractures
- C. Reduction in the frequency of fractures over time
- D. Improvement after menopause

Answer: B

Bone Loss Posttransplant
- Bone mass decreases 6-10% in first year
- Bone loss continues after that but at a slower rate
- In long term renal transplants, 40-60% have osteoporosis
- Fractures occur in 8% within 8 years (more common in diabetics)
- Foot is the most common fracture site

WHO Definitions

<table>
<thead>
<tr>
<th>OSTEOPENIA</th>
<th>OSTEOPOROSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>T score =  -1 and -2.5</td>
<td>T &lt; -2.5</td>
</tr>
</tbody>
</table>

T = number of SD a BMD value deviates from sex & age matched controls

Contributing Factors

- Underlying renal osteodystrophy
- Immunosuppressants (steroids and calcineurin inhibitors)
- Persistent hyperparathyroidism
- Gonadal status
- Age
- Gender
- Smoking
- Genetic predisposition
**Post transplant bone loss**

<table>
<thead>
<tr>
<th>Etiology of bone loss</th>
<th>Location of fracture</th>
<th>Predictive value of BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism</td>
<td>Appendicular spine and hip</td>
<td>?? Predicts risk of fracture</td>
</tr>
<tr>
<td>Adynamic bone</td>
<td></td>
<td>Predicts risk of fracture</td>
</tr>
<tr>
<td>Osteomalacia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Post menopausal osteoporosis**

<table>
<thead>
<tr>
<th>Etiology of bone loss</th>
<th>Location of fracture</th>
<th>Predictive value of BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism</td>
<td>Spine and hip</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Treatment**

- **Osteopenia**
  - T-score -1 to -2.5
  - 1200 mg Ca²⁺/day
  - 400-800 mcg vit D/day
  - Exercise
  - Hormone replacement
  - Vitamin D analogs

- **Osteoporosis**
  - T-score < -2.5

**Interim Summary**

- Board Review Points
  - Nonimmune factors associated with CAN: IR injury, CNI therapy, Hypertension
  - Most common posttransplant malignancies related to viral infection
  - Most common posttransplant cancer—nonmelanoma skin cancer (squamous cell > basal)
  - Rapid bone loss (within 6 months of transplantation - multifactorial)

- Update Points
  - Conversion from CNI to sirolimus for CAN may not be effective with pre-existing proteinuria or GFR < 40
  - TOR inhibitors effective in treatment of Kaposi’s sarcoma, RCC, and nonmelanoma skin cancer
  - Pre-existing or de novo anti-HLA antibodies increase the risk of graft loss

**Relisting for Transplant and Transplant Rates**

- Historically, around 40% of patients with failed transplants are relisted
- Kidney retransplantation shows similar survival benefits as the original transplant
- However, less than half of those relisted go on to receive new kidney transplants within 5 years

**Increased Mortality after Allograft Failure**

- USRDS data
- 78564 Kidney Transplant Recipients from 1988 to 1998
- Analyzed if survived > 1 month after allograft failure
- Two fold higher death rate than patients on waiting list
- Four fold higher risk of infection-related mortality

**Bisphosphonates for Posttransplant Osteopenia**

- Effective in increasing bone density
- Little evidence for reducing risk of fractures
- High incidence of inducing adynamic bone disease


Risk of Continuing Immunosuppressive Therapy after a Failed Kidney Transplant

Group A – early discontinuation
Group B – late discontinuation


Post-transplant inflammation and effect of transplant nephrectomy


Nephrectomy after Kidney Transplant Failure

● USRDS; 10,951 patients with failed kidney transplants returning to dialysis b/w 1/94 and 12/04; 3451 (31.5%) received transplant nephrectomies
● 32% reduction in relative risk of all cause mortality in the nephrectomy group
● Retransplantation rate
  • Nephrectomy group 10% p<0.001
  • Non-nephrectomy group 4.1%


Does Nephrectomy Lead to Alloantibody Sensitization?

● Study of 31 patients with allograft nephrectomy
  – 22 due to symptoms
  – 9 due to primary nonfunction
  – Pre PRA sample 304 ± 556 days before nephrectomy
  – Post PRA sample 234 ± 369 days after nephrectomy
● Increased in PRA after nephrectomy
  – Class I mean 33.4% to 75.6%
  – Class II mean 38.9% to 60.6%
  – Increase in donor specific antibody also noted

Knight MG et al. Urology 78: 314-18, 2011

Interim Summary

● Board Review Points
  – Patients with failed allografts have high mortality rates
  – Infection is the most common cause of death after a failed transplant
● Update Points
  – Role of allograft nephrectomy in management of the failed allograft is controversial
  – Both weaning of immunosuppression and allograft nephrectomy may increase rates of HLA sensitization