Principles of Immunosuppression
Karen Hardinger, PharmD, BCPS
Corticosteroids

**Mechanism:**
- Inhibits production of T-cell lymphokines (IL-1, IL-2, IL-6, gamma-interferon, and TNF-alpha)
- Causes emigration of circulating T-cell from intravascular tissue compartment to lymphoid tissue

**Dose:**
- Varies from center to center as well as organ to organ
- Induction - high doses tapered quickly over weeks
- Maintenance - typically 0.1 mg/kg/day, ?withdrawal
- Rejection - High dose, 250 - 1000 mg/d for 3 days

Corticosteroids: The Good versus The Bad

- ☑ Mechanism of action
- ☑ Few drug interactions
- ☑ Experience
- ☑ Cheap
- ☑ Convenient dosing

Side Effects
- ☑ Psychosis
- ☑ HTN
- ☑ Peptic ulcer
- ☑ Sodium and fluid retention
- ☑ Osteoporosis
- ☑ Hypercholesterolemia
- ☑ Impaired wound healing
- ☑ Weight gain
- ☑ Diabetes mellitus
Corticosteroids: Side Effects

- CNS - headache, convulsion
- Psychiatric - mood disturbances, psychosis
- HEENT - cataracts, glaucoma
- Endocrine - suppression of growth, menstrual irregularities
- CV - hypertension, sodium and fluid retention
- GI - peptic ulcer disease, abdominal distention, pancreatitis
- Renal - sodium and fluid retention, hypokalemic alkalosis, hypokalemia
- Musculoskeletal - osteoporosis, muscle weakness, steroid myopathy, loss of muscle mass
- Skin - impaired wound healing, fragile skin, acne
- Metabolic - increased appetite, weight gain, glucose intolerance, abnormal fat distribution

Case

J.W. is a 25 yo WM with ESRD secondary to HTN. He received a LRD kidney transplant. He is now 6 months post-transplant. At the clinic today his laboratory was WNL, SCr 1.1. His immunosuppression consists of CyA 200 mg bid, AZA 150 mg qd and prednisone 20 mg. He complains of difficulty sleeping and weight gain.

Which medication could be implicated?
Azathioprine (Imuran®)

- **Mechanism:**
  - A thiopurine analog converted to the active form 6-mercaptopurine which inhibits DNA and RNA synthesis by preventing the formation of adenylic and quanylic acids from inosinic acid

- **Dose:** Maintenance - 0.5-2.5 mg/kg

- **Side Effects:**
  - Dose-related
  - Dermatological - alopecia, increased risk of skin cancer
  - GI - pancreatitis, hepatotoxicity
  - Hematological - leukopenia, thrombocytopenia

azathioprine 50 mg tab
Case

M.K. is a 65 yo BM transplanted on 5-97 for ESRD secondary to diabetes mellitus. His WBC count is 1.3 and platelets 52. Viral work-up is negative and his only complaint is minor joint pain that has improved over the past month.

His medications include:
Prograf, Imuran, prednisone, Septra DS, Prilosec, Magnesium, Calcium, Multivitamin, NPH insulin

What changes in medication would you suggest?

Azathioprine Metabolism

Azathioprine → GST → 6-MP → Xanthine Oxidase → Thiouric acid

Drug interaction with Allopurinol

6-MMP → HGPRT → 6-TGNs
Mycophenolate Mofetil

- **Mechanism:**
  - Inhibition of IMPDH results in interference of the de novo pathway of quanine nucleotide synthesis and DNA replication

- **Indications:**
  - prevention of acute rejection, prevention of chronic rejection?

- **Dose:**
  - Maintenance: 2-3 gm/d

- **Side Effects:**
  - CNS - headaches
  - GI - diarrhea, nausea and vomiting
  - Hematological - bone marrow suppression
  - Other - increased risk of infections?

Antimetabolite
Azathioprine versus Mycophenolate

- **Mechanism:**
  - A thiopurine analog which inhibits DNA and RNA

- **Dose:** QD

- **Side Effects:**
  - Derm - alopecia, skin cancer?
  - GI – diarrhea, N/V pancreatitis, hepatotoxicity
  - Hematological

- **Cost:** $

- **Efficacy:** +

- **Mechanism:**
  - Inhibition of IMPDH results in interference DNA replication

- **Dose:** BID

- **Side Effects:**
  - CNS - headaches
  - GI - diarrhea, N/V
  - Hematological
  - Other - infections/skin ca?

- **Cost:** $$$

- **Efficacy:** +++
T.B. is a 55 yo BF transplanted 5-95 for ESRD secondary to SLE. She had two acute rejection episodes on 9-95 and 5-00. Her immunosuppression regimen includes tacrolimus 2 mg bid (levels 8-10ng/ml), MMF 1 gm bid and prednisone 10 mg qd. Other meds include Septra, Pecid, Norvusc, Magnesium and Multivitamin. She complains of nausea and diarrhea.

What medications adjustments would you suggest?

---

**Cyclosporine**

- **Sandimmune® - Cyclosporine oral solution**
  - Wide intra and interpatient variability
  - Absorption dependent on bile production

- **Neoral® - Cyclosporine microemulsion**
  - Improved absorption and bioavailability
  - Absorption independent of bile production

- **Gengraf® - Cyclosporine modified**
  - Branded generic, bioequivalent to Neoral®
Cyclosporine Formulations

- **Sandimmune® - Cyclosporine**
  - Wide intra and interpatient variability
  - Absorption dependent on bile production
  - Non-linear & unpredictable relationship between dose and level

- **Neoral® - Cyclosporine microemulsion**
  - Improved absorption and bioavailability
  - Better correlation with pharmacokinetic parameters

- **Cyclosporine modified**
  - Gengraf® Branded generic, bioequivalent to Neoral®
  - Cheaper alternative

<table>
<thead>
<tr>
<th>%Utilization</th>
<th>All organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-10%</td>
<td>80-85%</td>
</tr>
<tr>
<td></td>
<td>5-10%</td>
</tr>
</tbody>
</table>

Cyclosporine

- **Mechanism:**
  - inhibits T lymphocyte proliferation by prevention the production of IL-2

- **Indication:** Prophylaxis of rejection

- **Dose:**
  - Initial dose - 5-8 mg/kg/d divided twice daily, target trough concentration 250-350 ng/ml
  - Maintenance - target trough concentration 150-250 ng/ml

- **Side Effects:**
  - CNS - confusion, hallucinations, convulsion
  - HEENT - alopecia, gingival hyperplasia
  - CV - hypertension, hyperlipidemia
  - GI - nausea, diarrhea, hepatotoxicity, glucose interance
  - Renal - nephrotoxicity, ↓Mg, ↑K, hyperuricemia
  - Skin - acne, hirsutism
Cosmetic adverse events
- Relative absence of hirsutism and gingival hyperplasia in multiple transplant types

Before Prograf Conversion

Following Prograf Conversion

5 Boucher A. Service de Néphrologie. Hôpital Maisonneuve-Rosemont, QC.

C2 International Consensus Statement

- \( C_0 \) does not correlate well with \( AUC_{0.4} \)
- \( C_2 \) is the best single time-point predictor of \( AUC_{0.4} \)

Kidney
- Higher \( C_2 \) correlates with lower acute rejection rates

Liver
- \( C_2 \) improves renal function, reduce HTN
- An association with \( C_2 \) and chronic rejection

CT/Pancreas- not established

Dose:
- \( C_2 \) - 15 minute window
- Initial \( C_2 \) 800-1700 ng/ml, maint - 600-1200 ng/ml

BJC Protocol

Kidney
- Initial 1000-1200 ng/ml, maint. - 600-1000 ng/ml

Liver
- Initial \( C_2 \) 800-1200 ng/ml, maint. - 600-1000 ng/ml

Levy, Transplantation 2002;73:s12
Sirolimus: FKBP12 Complex Has No Effect on Calcineurin Activity

## CyA Afferent Vasoconstriction

### Drug Interactions

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inducer of CYP3A enzyme</td>
<td>Phenytoin, Phenobarbitol, Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>St. John’s Wort</td>
</tr>
<tr>
<td></td>
<td>Rifampin, Isoniazid</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole, Fluconazole, Itraconazole, Voriconazole</td>
</tr>
<tr>
<td></td>
<td>Macrolide antibiotics</td>
</tr>
<tr>
<td></td>
<td>Erythromycin, Clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td></td>
<td>Verapamil, Diltiazem, Nicardipine</td>
</tr>
<tr>
<td></td>
<td>Grapefruit Juice</td>
</tr>
<tr>
<td>Inhibitor of CYP3A enzyme</td>
<td>HMG-CoA reductase inhibitors</td>
</tr>
<tr>
<td>Substrate of CYP3A enzyme</td>
<td>Magnesium Oxide, Cholestyramine</td>
</tr>
<tr>
<td>Interference with absorption</td>
<td></td>
</tr>
</tbody>
</table>
Tacrolimus, Prograf®, FK-506

- **Mechanism:**
  - A macrolide antibiotic which inhibits T lymphocyte proliferation by preventing the production and secretion of IL-2

- **Indication:** prevention of acute rejection

- **Dose:**
  - Initial - 0.05-0.10 mg/kg/d in two divided dose with target trough concentrations 10-15 ng/ml
  - Maintenance - target trough concentration 5-10 ng/ml

<table>
<thead>
<tr>
<th>Prograf</th>
<th>0.5 mg</th>
<th>1 mg</th>
<th>5 mg</th>
</tr>
</thead>
</table>

Cyclosporine versus Tacrolimus

- **Formulation:** capsule, IV, soln
- **Dose:**
  - Initial – 4-10 mg/kg/d in two doses
  - Target trough concentrations 250-350 ng/ml
  - Maintenance - target trough concentration 150-250 ng/ml

- **Indication:** prevention of acute rejection

- **Formulation:** capsule, IV
- **Dose:**
  - Initial - 0.05-0.10 mg/kg/d in two doses
  - Target trough concentrations 10-15 ng/ml
  - Maintenance - target trough concentration 5-10 ng/ml

- **Indication:** prevention of acute rejection
Cyclosporine versus Tacrolimus

Side Effects:
- CNS - confusion, hallucinations, convulsion
- HEENT - hirsutism, gingival hyperplasia
- CV - hypertension, hyperlipidemia
- GI - nausea, diarrhea, hepatotoxicity
- Metabolism - glucose intolerance
- Renal - nephrotoxicity, ↓Mg, ↑K, hyperuricemia
- Skin - acne

Side Effects:
- CNS - confusion, hallucinations, convulsion
- HEENT - alopecia
- CV - hypertension, hyperlipidemia
- GI - nausea, diarrhea, hepatotoxicity
- Metabolism - glucose intolerance
- Renal - nephrotoxicity, ↓Mg, ↑K, hyperuricemia
- Skin - acne

Summary of Adverse Effects

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Hypertension</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>GI Toxicity</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cosmetic</td>
<td>Hirsutism Hyperplasia</td>
<td>Alopecia</td>
</tr>
</tbody>
</table>
Efficacy: Neoral vs Prograf

- **European:**
  - Lower acute rejection with tacrolimus vs Neoral, 20% vs 37%, respectively
  - Similar patient and graft survival at 6 months

- **United States:**
  - Rejection rates were similar in each group (<20%)
  - Lower corticosteroid resistant rejection in the tacrolimus arms


Calcineurin Inhibitor:

Tacrolimus versus Cyclosporine

- Efficacy
- Cosmetic ADRs
- Experience
- Cosmetic ADRs
- $$$ Expensive
- Drug Monitoring

---

15
Calcineurin Inhibitor:
The Good versus The Bad

- Mechanism of action
- Efficacy
- Experience
- Clinical Data

- Side effects
- $$$$$ Expensive
- Drug interactions
- Monitoring

Sirolimus, Rapamune®, rapamycin

- **Mechanism:**
  - Binds to FKBP-12 and inhibits mTOR, cell cycle arrest in G1-S phase
  - Sirolimus inhibits T-cell proliferation and cytokines (IL-2, IL-4, IL-6)

- **Dose:**
  - Loading dose - 3x maintenance, Maint. - 2-5 mg/d, Role of TDM???

- **Side Effects:**
  - CNS - headache
  - CV - hypertriglyceridemia, hypercholesterolemia
  - GI - diarrhea, nausea
  - Hematological - leukopenia, thrombocytopenia, anemia, thrombosis
  - Other – dehiscence, lymphocele, mouth sores, hepatic artery thrombois

- **Costs: $$$$$, Efficacy: ????**

Sirolimus 1 mg tab, oral solution 1mg/ml
## Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Sirolimus</th>
<th>Tacrolimus</th>
<th>Cyclosporine (Neoral)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to Peak</strong></td>
<td>0.8-3 h</td>
<td>1-3 h</td>
<td>1.5-2 h</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>15-20%</td>
<td>17-31%</td>
<td>--</td>
</tr>
<tr>
<td><strong>Protein Binding</strong></td>
<td>--</td>
<td>99%</td>
<td>90%</td>
</tr>
<tr>
<td><strong>Vd</strong></td>
<td>5.6 – 16.7 L/kg</td>
<td>0.85 – 1.91 L/kg</td>
<td>3 – 5 L/kg</td>
</tr>
<tr>
<td><strong>Blood : Plasma</strong></td>
<td>10-40</td>
<td>12-67 (mean 35)</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Liver</td>
<td>Liver</td>
<td>Liver</td>
</tr>
<tr>
<td><strong>Clearance</strong></td>
<td>147 – 240 mL/h/kg</td>
<td>40-53 mL/h/kg</td>
<td>354 – 516 mL/h/kg</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Bile</td>
<td>Bile</td>
<td>Bile</td>
</tr>
<tr>
<td><strong>Elimination t1/2</strong></td>
<td>57 - 63 h</td>
<td>8-12 h</td>
<td>8 h</td>
</tr>
</tbody>
</table>

---

**Sirolimus: FKB12 Complex Has No Effect on Calcineurin Activity**

Binding protein

- Cyclophilin

Effector protein

- Calcineurin
  - Inhibit
  - IL-2 message
  - \( G_0 \) [arrows] \( G_1 \)

- mTOR
  - Inhibit
  - IL-2 response
  - \( G_1 \) [arrow] \( S \)

---

### Binding Proteins

<table>
<thead>
<tr>
<th>Binding Protein</th>
<th>Cyclophilin</th>
<th>FKBP</th>
<th>FKBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effector Protein</td>
<td>Calcineurin</td>
<td>Calcineurin</td>
<td>mTOR</td>
</tr>
<tr>
<td>IL-2 message</td>
<td>Inhibited</td>
<td>Inhibited</td>
<td></td>
</tr>
<tr>
<td>IL-2 response</td>
<td></td>
<td></td>
<td>Inhibited</td>
</tr>
<tr>
<td>Cell-cycle effect</td>
<td>$G_0-G_1$</td>
<td>$G_0-G_1$</td>
<td>$G_1-S$</td>
</tr>
</tbody>
</table>

### Sirolimus: Drug Interactions

- Similar P450 3A4 interactions, like CsA/ FK506

- When administered *simultaneously* with CsA versus alone:
  - sirolimus peak levels $\uparrow$ 116% and the AUC $\uparrow$ 230%

- When administered *4 hours* after CsA versus alone:
  - sirolimus peak levels $\uparrow$ 37% and the AUC $\uparrow$ 80%

To avoid this drug interaction, sirolimus should be taken four hours after CsA or at least consistently.
# Differential Drug Interactions

## Sirolimus
- Increases CsA levels; increases sirolimus levels particularly if given simultaneously.
- Decreases Tac levels.
- No apparent effect on sirolimus levels.

## Mycophenolate Mofetil
- Decreases MPA levels due to inhibition of enterohepatic recirculation.
- No effect on Tac levels.
- No effect on MPA levels.

### Cyclosporine

### Tacrolimus

## Sirolimus Hepatic Artery Thrombosis - Black Box
- Two multicenter, randomized studies of de novo liver transplant recipients.
- Sirolimus associated with increase in hepatic artery thrombosis.
- Most occurred within 30 days of transplant.
- Most lead to death or graft loss.

### Phase II studies:
- SRL/TAC/steroid vs TAC/steroid - HAT 6/110 (5.5%) vs 1/112 (0.9%).
- SRL/CsA/steroid vs CsA/steroid - HAT 10/112 (8.9%) vs 2/52 (3.8%).

Sirolimus is not approved in liver transplantation.
Sirolimus prevents intimal proliferation

Smooth muscle cell α-actin staining of aortic segments in cynomolgus monkeys removed on day 105. Brown staining indicates positive cells. A. A native aortic segment exhibited uniform smooth muscle cell α-actin staining of the media. No intimal thickening was present. The adventitia had positive staining in the vasa vasorum (x40). B. Marked concentric intimal proliferation contained abundant smooth muscle cells/myofibroblasts in an allograft segment from an untreated monkey. In contrast, the media had only minimal amount of α-actin positive cells. (x30). C. In the allograft intima from a sirolimus-treated monkey there was mild concentric smooth muscle cells/myofibroblast proliferation, mainly located on the left half of the circumference in the figure. Unlike in the allografts removed from untreated animals, numerous α-actin positive cells were seen in the media after sirolimus treatment (x30). D. Another allograft from a sirolimus-treated monkey had minimal intimal layer without remarkable α-actin staining. The media exhibited numerous α-actin positive cells (x30).

Transplantation 2000; 70:969

Summary of Immunosuppressive Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>CsA</th>
<th>FK</th>
<th>AZA</th>
<th>MMF</th>
<th>Pred</th>
<th>Rapa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>+</td>
<td>+++</td>
<td></td>
<td></td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Bone Marrow Suppression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Toxicity</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>+</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
Antithymocyte globulin

- Atgam® - Antithymocyte globulin derived from horse
  - Dose:
    - Treatment: 15 mg/kg/d x 7-14 days, monitor CD2/CD3

- Thymoglobulin® - Antithymocyte globulin derived from rabbit
  - Dose:
    - Induction 1.5 mg/kg x 3-7 days
    - Treatment 1.5 mg/kg x 7-14 days, monitor CD2
Antithymocyte globulin

- **Mechanism:**
  - Antibodies interact with lymphocyte surface antigens, depleting numbers of circulating thymus-derived lymphocytes
  - Lymphocyte depletion by complement-dependent lysis or opsonization and phagocytosis by macrophages that prevent T-cell proliferation
  - Thymoglobulin consist of antibodies specific for T-cell epitopes including CD2, CD3, CD4, CD8 and CD25
Antigen Presentation

Antithymocyte globulin

◆ Side Effects:
  - Dermatologic - rash
  - Immunologic - cytokine release syndrome
  - Hematologic - leukopenia, thrombocytopenia, lymphoproliferative disease
  - Other - increased risk of infection
The Risk of Acute Rejection Remained Less with Thymoglobulin at 2 years

Cumulative Risk of Acute Rejection (%)

Days

log rank test = 6.3
p = 0.0119

Atgam (n = 24)

Thymoglobulin (n = 48)

27%

6%

Uncensored* Graft Survival Remained Better with Thymoglobulin at 2 Years

Graft Survival, %

Days

log-rank test, 3.7
p = 0.054

Atgam (n=24)

Thymoglobulin (n=48)

94%

79%

*Patient death included as graft loss
At five years after transplantation, the composite endpoint of freedom from death, graft loss, or rejection, event-free survival, was superior with Thymoglobulin (73%) compared to Atgam (33%; P < 0.001).

Figure 2. Patient and Graft Survival. Despite a small number of patients treated, graft survival was significantly better in the Thymoglobulin arm (79%) versus the Atgam arm (58%; P=0.026).
**THYMOGLOBULIN vs ATGAM INDUCTION**

*Leukocyte Response*

---

**Absolute Lymphocyte Count**

**Granulocyte Count**

**White Blood Cell Count**

---

**Lymphocyte Depletion was More Durable**

*With Thymoglobulin*

---

* p<0.007 Wilcoxon Rank Sum test
Thymoglobulin Patients Had Long-term Suppression of CD4

Results are means measured at a mean follow up of 22 months

Muromonab-CD3, Orthocline®, OKT3

◆ Mechanism:
  - OKT3 binds to the CD3 receptor complex on T-lymphocytes, and prohibits antigen recognition
  - OKT3 induces lymphocyte opsonization and phagocytosis and prevents their proliferation T-lymphocytes

◆ Indication: treatment of steroid-resistant rejection

◆ Dose:
  - Caution - Prior to administration evaluate volume status for evidence of fluid overload or uncompensated heart failure
  - Treatment - 5 mg iv x 10-14 days
  - Premedication - steroids, acetaminophen, diphenhydramine
Muromonab-CD3

◆ Side Effects:
  - CNS - headache
  - HEENT - photophobia
  - CV - chest pain, hypertension, pulmonary edema
  - GI - nausea, vomiting, diarrhea
  - Musculoskeletal - rigor, tremor
  - Other - cytokine release syndrome, hypersensitivity

Basiliximab/ Daclizumab

Mouse

Human

Chimeric Simulect

Humanized Zenapax
Basiliximab/ Daclizumab

**Simulect®** - basiliximab, chimeric (human and murine) monoclonal antibody
- Dose - 20 mg iv prior to transplant and a second 20 mg dose four days after transplant

**Zenapax®** - daclizumab, humanized monoclonal antibody
- Dose
  - Packet insert - 1 mg/kg iv prior to transplant and every 14 days for a total of five doses
  - Alternate dosing strategies - 2 mg/kg x 2 doses

**Mechanism:**
- Binds to a subunit on the IL-2 receptor, thus blocking the IL-2 receptor complex and inhibiting IL-2 binding capacity and T-lymphocyte proliferation

**Side Effects:** Generally well-tolerated

---

**Antibody Agents**

**ATG** versus **IL-2RA**

**Available Agents**
- **Atgam** – ATG horse
  - 15 mg/kg/d x 7-14 days
- **Thymoglobulin** – ATG rabbit
  - 1.5 mg/kg x 7-14 days
- **OKT3** – murine
  - 5 mg x 7-14 days

**Side Effects:**
- Dermatologic - rash
- Immunologic - cytokine release syndrome
- ATG - Hematologic
- OKT3 – headaches, pulm.edema
- Other - increased risk of infection

**Efficacy:** improved?

**Available Agents**
- **Simulect** – basiliximab
  - Dose - 20 mg iv POD 0 & 4
- **Zenapax** – daclizumab
  - Dose- 1 mg/kg iv prior to transplant and q14 days x 5
  - Alternate dosing strategies - 2 mg/kg x 2 doses

**Side Effects:** Generally well-tolerated
Induction Agents: The Good versus The Bad

- Mechanism of action
- Efficacy
- Experience?
- Drug interactions

- Side effects
- Cancer
- Infection
- $$$ Expensive

Pharmacoeconomic Considerations

Estimated Annual Expenditures for Selected Immunosuppressants in the US (2000 Dollars)

- Tacrolimus: $166 million
- Daclizumab: $15 million
- Basiliximab: $14 million
- MMF: $168 million
- Sirolimus: $12 million
- Sandimmune and Neoral: $353 million
- Generic CyA-Modified Solutions: $10 million

Total = $738 million

Source: IMS Health
## Medication Dose Cost/month

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Cost/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine (Neoral)</td>
<td>300 mg BID</td>
<td>$1,273</td>
</tr>
<tr>
<td>Tacrolimus (Prograf/FK-506)</td>
<td>3 mg BID</td>
<td>$511</td>
</tr>
<tr>
<td>Tacrolimus (Prograf/FK-506)</td>
<td>5 mg BID</td>
<td>$833</td>
</tr>
<tr>
<td>Sirolimus (Rapamune)</td>
<td>2 mg QD</td>
<td>$384</td>
</tr>
<tr>
<td>Sirolimus (Rapamune)</td>
<td>5 mg QD</td>
<td>$960</td>
</tr>
<tr>
<td>Azathioprine (Imuran)</td>
<td>150 mg QHS</td>
<td>$72</td>
</tr>
<tr>
<td>Tacrolimus (Prograf/FK-506)</td>
<td>3 mg BID</td>
<td>$511</td>
</tr>
<tr>
<td>Tacrolimus (Prograf/FK-506)</td>
<td>5 mg BID</td>
<td>$833</td>
</tr>
<tr>
<td>Sirolimus (Rapamune)</td>
<td>2 mg QD</td>
<td>$384</td>
</tr>
<tr>
<td>Sirolimus (Rapamune)</td>
<td>5 mg QD</td>
<td>$960</td>
</tr>
<tr>
<td>Mycophenolate (Cellcept)</td>
<td>1 gm BID</td>
<td>$537</td>
</tr>
<tr>
<td>Prednisone (Deltasone)</td>
<td>20 mg QD</td>
<td>$8</td>
</tr>
<tr>
<td>Ganciclovir (Cytovene)</td>
<td>1000 mg TID</td>
<td>$1,410</td>
</tr>
<tr>
<td>SMZ 800/TMP 160 (Septra)</td>
<td>1 tab QHS</td>
<td>$11</td>
</tr>
<tr>
<td>Acyclovir (Zovirax)</td>
<td>200 mg bid</td>
<td>$15</td>
</tr>
<tr>
<td>Nystatin (Mycostatin)</td>
<td>5 ml QID</td>
<td>$30</td>
</tr>
<tr>
<td>Neoral+AZA+pred+ganciclovir+nystatin+Septra</td>
<td>$2,804</td>
<td></td>
</tr>
<tr>
<td>FK+MMF+pred+ganciclovir+nystatin+Septra</td>
<td>$2,829</td>
<td></td>
</tr>
</tbody>
</table>

## BJC and Patient Charges

<table>
<thead>
<tr>
<th>BJC</th>
<th>Cost/Vial</th>
<th>Dose</th>
<th>Cost/Dose (70kg)</th>
<th>Duration</th>
<th>Cost/Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atgam</td>
<td>$ 205</td>
<td>15 mg/kg</td>
<td>$ 818</td>
<td>4 days</td>
<td>$ 3,272.48</td>
</tr>
<tr>
<td>Thymoglobulin</td>
<td>$ 201</td>
<td>1.5 mg/kg</td>
<td>$ 804</td>
<td>4 days</td>
<td>$ 3,215.20</td>
</tr>
<tr>
<td>OKT3</td>
<td>$ 650</td>
<td>5 mg</td>
<td>$ 650</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zenapax</td>
<td>$ 339</td>
<td>1 mg/kg</td>
<td>$ 1,017</td>
<td>5 doses</td>
<td>$ 5,085.00</td>
</tr>
<tr>
<td>Simulect</td>
<td>$1,159</td>
<td>20 mg</td>
<td>$ 1,159</td>
<td>2 doses</td>
<td>$ 2,318.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cost/Vial</th>
<th>Dose</th>
<th>Cost/Dose</th>
<th>Duration</th>
<th>Cost/Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atgam</td>
<td>$ 430</td>
<td>15 mg/kg</td>
<td>$ 1,718</td>
<td>10 days</td>
<td>$ 17,180.00</td>
</tr>
<tr>
<td>Thymoglobulin</td>
<td>$ 434</td>
<td>1.5 mg/kg</td>
<td>$ 1,734</td>
<td>10 days</td>
<td>$ 17,340.00</td>
</tr>
<tr>
<td>OKT3</td>
<td>$ 875</td>
<td>5 mg</td>
<td>$ 875</td>
<td>10 days</td>
<td>$ 8,750.00</td>
</tr>
</tbody>
</table>
**Summary:**
Nationwide Immunosuppressive Regimens

<table>
<thead>
<tr>
<th>Organ</th>
<th>Induction</th>
<th>Calcineurin Inhibitor</th>
<th>Anti-metabolite</th>
<th>Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>40% IL2RA 20% ATG</td>
<td>40% Tacrolimus 60% Cyclosporine</td>
<td>50% Mycophenolate</td>
<td>60%</td>
</tr>
<tr>
<td>Liver</td>
<td>10% IL2RA</td>
<td>Tacrolimus</td>
<td>50% Mycophenolate 50% none</td>
<td></td>
</tr>
<tr>
<td>SKP</td>
<td>50% IL2RA 35% ATG</td>
<td>Tacrolimus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>20% IL2RA 25% ATG</td>
<td>Tacrolimus 30% Cyclosporine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>25% IL2RA 15% ATG</td>
<td>Tacrolimus 50% Cyclosporine</td>
<td>50% Mycophenolate 50% none</td>
<td></td>
</tr>
</tbody>
</table>

**OPTN/SRTR Annual Report 2002**

---

**Patient Counseling**

- Why do I have to take this medicine?
- How can I remember to take these medicines?
- When should I take my medicines?
- What do I do if I have side effects?
- Can I take other medications?
- Can I take OTC medications?
- What should I do if I miss a dose?
- Can I use generic medications?
Patient Counseling

- Grapefruit and grapefruit juice interfere with this medication, therefore it should be avoided.
- Your dose may be changed based on blood levels of this medication. Always have blood drawn 12 hours after your last dose. Wait to take your morning dose until after your blood draw.

Future Agents?

- SDZ-RAD
- Inhibitors of Tcell target Janus Kinase 3, AG490
- C-raf isoform specific enzymes
- Selectin blocking agents
- Anti-ICAM-1 antisense deoxy oligonucleotides
- Lymphocyte homing inhibitor FTY720
- Tolerance
- Gene therapy