Objectives

- Identify common immunosuppressive medication regimens utilized in abdominal solid organ transplantation
- Counsel on the most common adverse effects associated with each immunosuppressive agent
- Interpret pharmacokinetic and pharmacodynamic drug-drug and drug-disease interactions

The Immune Response

Mechanisms of T-Cell Activation

Balancing Act of Transplant

Maintenance Immunosuppression
Immunosuppressive Regimens

<table>
<thead>
<tr>
<th>Primary Agent</th>
<th>Second Agent</th>
<th>Third Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>Mycophenolate mofetil</td>
<td>± Prednisone</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Mycophenolate sodium</td>
<td></td>
</tr>
<tr>
<td>Belatacept</td>
<td>Azathioprine</td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Everolimus</td>
<td></td>
</tr>
</tbody>
</table>

Tacrolimus and Cyclosporine

Available Oral Tacrolimus Products

Tacrolimus (Prograf®)

- **Category**: Adult Dosing
- **Description**: 0.1–0.2 mg/kg/day in two equally divided doses
- **Administration considerations**: Administered twice daily at least 12 hours apart
- **Formulations**: Capsule, oral solution (compounded), intravenous injection
  - *Powder from capsules may also be administered sublingually*
- **Monitoring**: Trough monitoring required (5–12 ng/mL)
  - Correlation with efficacy and toxicity

Tacrolimus XL (Astagraf®)

- Prolonged-release formulation delivers active drug over 24 hours
  - Administered once daily in the morning on an empty stomach
  - Likely non-formulary at most institutions

- **Not indicated in liver transplantation**

- **Contraindicated with alcohol**
  - Dumping phenomenon

*Source: N Engl J Med 2004;351:2715-29*
Pharmacokinetic Changes with Astagraf®

Tacrolimus IR (Prograf®)
Tacrolimus XL (Astagraf®)

Accessed from: http://www.lcpharma.com/portfolio.cfm

Patients who are NPO or unable to receive oral suspension (NG tube access)
- Use capsules NOT suspension
- Administration procedure
  - Open capsule and administer contents directly under tongue
  - Instruct patient not to swallow
  - No food or drink for 20 minutes after administration
- Bypass first pass effect through liver
- Anticipate dose adjustment to ½ current dose if patient remains on SL administration long-term

Sublingual Administration of Tacrolimus

Available Oral Cyclosporine Products

Cyclosporine (Neoral®, Sandimmune®)

Category | Description
---|---
Adult Dosing | • 5-10mg/kg/day orally in two equally divided doses
• IV dose is 1/3 of total oral daily dose
Administration considerations | • Administered twice daily at least 12 hours apart
• Oral solution should be administered in a glass with appropriate liquid
  - Neoral® – room temperature orange or apple juice
  - Sandimmune® – room temperature milk, chocolate milk or orange juice
Formulations | • Capsule, oral solution, intravenous injection
Monitoring | • Trough and 2 hour peak (C2) levels used for monitoring
  - C2's have better correlation with AUC but are impractical

Cyclosporine Formulation Differences

MODIFIED (Neoral®, Gengraf®) Non-modified (Sandimmune®)

MODIFIED vs. Non-modified
- More consistent absorption
- Absorption less dependent on bile
- Rapid achievement of peak concentrations

MODIFIED and Non-modified formulations are NOT interchangeable
- MODIFIED (Neoral®, Gengraf®) cyclosporine formulations are two times more bioavailable than the Non-modified (Sandimmune®) formulation
- Conversion between MODIFIED and Non-modified formulations
  - Patient is on Sandimmune® 100mg PO BID
  - Conversion to Neoral® would be 50mg PO BID
Calcineurin Inhibitor Level Monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>0-6 months</th>
<th>6-12 months</th>
<th>&gt; 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>B-10</td>
<td>6-8</td>
<td>4-8</td>
</tr>
<tr>
<td>Liver</td>
<td>B-10</td>
<td>6-8</td>
<td>4-6</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>250-350</td>
<td>100-150</td>
<td>100-150</td>
</tr>
<tr>
<td>Liver</td>
<td>200-250</td>
<td>100-150</td>
<td>80-125</td>
</tr>
</tbody>
</table>

**Target levels will vary depending on a patient's risk for rejection/infection or malignancy as well as their tolerance of other immunosuppressants**

Additional Cyclosporine Monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>0-6 months</th>
<th>6-12 months</th>
<th>&gt; 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>250-350</td>
<td>100-150</td>
<td>100-150</td>
</tr>
<tr>
<td>Liver</td>
<td>200-250</td>
<td>100-150</td>
<td>80-125</td>
</tr>
</tbody>
</table>

**Target levels will vary depending on a patient's risk for rejection/infection or malignancy as well as their tolerance of other immunosuppressants**

Calcineurin Inhibitors - Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Tacrolimus</th>
<th>Cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxicity</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Malignancy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HTN</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>DM</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Alopecia</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>GI disturbances</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hematologic abnormalities</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Gingival hyperplasia</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Tacrolimus vs. Cyclosporine

- Comparative studies in many organ transplant types
  - Kidney, liver, kidney/pancreas
- Higher rates of biopsy-proven acute rejection found in cyclosporine treated patients

<table>
<thead>
<tr>
<th>Study</th>
<th>N per group</th>
<th>Tacrolimus (TAC)</th>
<th>Cyclosporine (CsA)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramer, et al</td>
<td>237 TAC; 222 CsA</td>
<td>19.6% (0-6mo) 1.7% (7-12mo)</td>
<td>37.3% (0-6mo) 4.7% (7-12mo)</td>
<td>&lt;0.01 NS</td>
</tr>
<tr>
<td>Cheung, et al</td>
<td>38 TAC; 38 CsA</td>
<td>13.2% (1yr) 18.4% (~6yrs)</td>
<td>28.9% (1yr) 42% (~6yrs)</td>
<td>0.03 NR</td>
</tr>
</tbody>
</table>

NS: non-significant; NR: not reported

Mammalian Target of Rapamycin (mTOR) Inhibitors

- Sirolimus and Everolimus

Sirolimus & Everolimus

- Sirolimus & Everolimus
Common Indications for mTOR Inhibitors

- Nephrotoxicity from calcineurin inhibitors
  - Combination of sirolimus/everolimus + tacrolimus to allow for lower tacrolimus concentrations
- Intolerable adverse effects from calcineurin inhibitors
  - Complete switch to mTOR inhibitor based immunosuppression
- Active malignancy
  - Recurrent hepatocellular carcinoma is a common indication
  - Positive BK viral load/BK nephropathy
  - Complete switch to mTOR inhibitor based immunosuppression

Sirolimus (Rapamune®) & Everolimus (Zortress®)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dosing</td>
<td>Sirolimus: 2-6mg po daily</td>
</tr>
<tr>
<td></td>
<td>Everolimus: 0.75mg-1.25mg PO BID</td>
</tr>
<tr>
<td>Administration</td>
<td>Blood draws for trough levels must be drawn prior to the next dose</td>
</tr>
<tr>
<td>considerations</td>
<td></td>
</tr>
<tr>
<td>Formulations</td>
<td>Sirolimus: tablet, oral solution</td>
</tr>
<tr>
<td></td>
<td>Everolimus: tablet</td>
</tr>
<tr>
<td></td>
<td>Dispersible in water for ng/og tube administration</td>
</tr>
<tr>
<td>Pharmacokinetic</td>
<td>Half life [t1/2]:</td>
</tr>
<tr>
<td>differences</td>
<td>Sirolimus: ~ 70 hours</td>
</tr>
<tr>
<td></td>
<td>Everolimus: ~ 30 hours</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Trough monitoring</td>
</tr>
</tbody>
</table>

mTOR Inhibitors - Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>ACE Inhibitors</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Lipid lowering agents</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Rash/acne/oral ulcers</td>
<td>Topical steroids/ acne treatment</td>
</tr>
<tr>
<td>Impaired wound healing</td>
<td>Avoid for one month after transplant</td>
</tr>
<tr>
<td>Leukopenia/anemia</td>
<td>G-CSF</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>Ultrasound (hepatic &amp; renal arteries)</td>
</tr>
</tbody>
</table>

mTOR Inhibitor Level Monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>0-6 months</th>
<th>6-12 months</th>
<th>&gt; 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus</td>
<td>Trough level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>8-10</td>
<td>6-8</td>
<td>4-8</td>
</tr>
<tr>
<td>Liver</td>
<td>8-10</td>
<td>6-8</td>
<td>4-6</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Trough level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>6-8</td>
<td>4-6</td>
<td>3-5</td>
</tr>
<tr>
<td>Liver</td>
<td>6-8</td>
<td>3-5</td>
<td></td>
</tr>
</tbody>
</table>

Belatacept (Nulojix®)

Costimulation Blocker
Belatacept
Belatacept (Nulojix®)

**Adult dosing**
- Initial phase (10 mg/kg IV): Day 0, Day 4, end of week 2, week 4, week 8, and week 12 post transplant
- Maintenance phase (5 mg/kg IV): End of week 16 post transplant and every 4 weeks (± 3 days) thereafter

**Administration considerations**
- Dose should be divisible by 12.5 to facilitate accurate preparation with silicone free syringe
- Dose change only with a >10% change in weight
- Contraindicated in EBV negative patients

**Formulations**
- Intravenous infusion

**Adverse effects**
- Progressive multifocal leukoencephalopathy (PML), CNS post-transplant lymphoproliferative disorder, infections including tuberculosis

Antimetabolites

**Mycophenolate products and Azathioprine**

- **Mycophenolate Containing Products**
  - Mycophenolate sodium (Myfortic®)
    - Adult dosing
      - Cellcept® 500–1500 mg BID vs. Myfortic® 360–720mg BID
      - Cellcept 250mg = Myfortic 180mg
    - IV:PO conversion – 1 : 1
  - Cellcept® – capsule/tablet (250mg/500mg), oral suspension, IV
  - Myfortic® – enteric coated tablet
  - Adverse effects
    - Gastrointestinal disturbances (nausea, vomiting, heartburn, diarrhea), myelosuppression (especially leukopenia)
  - Monitoring
    - Not routine, Mini AUC if altered absorption suspected
    - MPA AUC = 7.75+6.49(c0h)+0.76(c0.5h)+2.43(c2h)

**Mycophenolate REMs**

- Approved by FDA in October 2012
- Established to ensure women of child bearing potential are aware of risks
- Prescribers and affiliated health care providers should be registered with FDA
- Patients of child bearing potential should sign a patient-prescriber agreement form acknowledging their understanding of the risks associated with mycophenolate
- Medication guide to be provided with all prescriptions
- All pregnancies must be reported to the mycophenolate pregnancy registry

**Mycophenolate REMs**

- The following table lists the forms of contraception that are acceptable for use during treatment with mycophenolate
  - Approved contraception methods
    -屏障方法
    - 子宫内避孕器
    - 皮下埋植法
    - 避孕药
    - 短效口服避孕药
    - 长效口服避孕药

- Provide education about emergency contraception
Azathioprine

**Adult dosing**
- 1-3 mg/kg orally once a day

**Administration considerations**
- Tablets should not be crushed

**Formulations**
- Oral tablets, oral suspension (compounded)

**Adverse effects**
- Thrombocytopenia, leukopenia, anemia, N/V/D

**Monitoring**
- Not necessary

Corticosteroids

**Adult dosing**
- Methylprednisolone – typically administered in OR at 500-1000mg then tapered to prednisone
- Prednisone – dosing and duration will vary depending on center protocol

**Administration considerations**
- If NPO convert prednisone to IV methylprednisolone
- 5:4 conversion ratio

**Formulations**
- Methylprednisolone – oral tablets and IV infusion
- Prednisone – oral tablets

**Adverse effects**
- Psychosis, weight gain, fluid retention, hyperglycemia, hypertension, osteoporosis, hyperlipidemia, insomnia

**Monitoring**
- Not necessary

Drug Interactions - CYP3A4 Inhibitors

**Increased levels of tacrolimus/cyclosporine/sirolimus/everolimus**
- Protease inhibitors – ritonavir, darunavir, fosamprenavir
  - Strivil® (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate)
- Azole antifungals – voriconazole, posaconazole, fluconazole, clotrimazole troche
- Non-dihydropyridine calcium channel blockers – diltiazem and verapamil
- Macrolide antibiotics – erythromycin, clarithromycin – NOT azithromycin
- Amiodarone
- Grapefruit /grapefruit juice
- Soda’s – Fresca, Blue Sky, IZZE, Hansen’s

Drug Interactions - CYP3A4 Inducers

**Decreased levels of tacrolimus/cyclosporine/sirolimus/everolimus**
- Anticonvulsants – phenytoin, phenobarbital (primidone), carbamazepine
- Nafcilin (more data with cyclosporine)
- Miscellaneous
  - Rifampin, rifabutin and rifapentine
  - St. John’s Wort
  - Fioricet (acetaminophen, butalbital, and caffeine)

Drug Interactions - Antimetabolites

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Immunosuppressant</th>
<th>Medications to avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased absorption</td>
<td>Mycophenolate products</td>
<td>Aluminum, magnesium, Calcium, iron phosphate binders (sevelamer carbonate, lanthanum carbonate)</td>
</tr>
<tr>
<td>Separated by 4 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interruption of enterohepatic recirculation</td>
<td>Mycophenolate products</td>
<td>Cholestyramine / Colesevelam / colestipol</td>
</tr>
<tr>
<td>Inhibition of absorption (pH dependent)</td>
<td>Mycophenolate mofetil</td>
<td>PPI’s (most data with esomeprazole, lansoprazole, omeprazole, pantoprazole)</td>
</tr>
<tr>
<td>Xanthine oxidase inhibition</td>
<td>Azathioprine</td>
<td>Allopurinol and febuxostat</td>
</tr>
</tbody>
</table>
Pharmacodynamic Interactions

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Immunosuppressant</th>
<th>Medications to avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhanced nephrotoxicity</td>
<td>Calcineurin inhibitors</td>
<td>NSAIDs, amphotericin B, aminoglycosides</td>
</tr>
<tr>
<td>Immune system stimulation</td>
<td>All</td>
<td>Herbals- ginseng, Echinacea, high dose Vitamin E, interferon</td>
</tr>
<tr>
<td>Gingival hyperplasia</td>
<td>Cyclosporine</td>
<td>Nifedipine and phenytoin</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Calcineurin inhibitors</td>
<td>Ace-inhibitors</td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>Mycophenolate products, Azathioprine</td>
<td>Valganciclovir, acyclovir, sulfamethoxazole/trimethoprim</td>
</tr>
</tbody>
</table>

Self Assessment Questions

Interpreting Tacrolimus Levels

- Mr Jones is s/p kidney transplant 3 weeks ago and is maintained on a regimen of tacrolimus 4 mg PO BID, mycophenolate mofetil PO 1000mg BID and prednisone 5 mg PO daily. The team calls you for advice in adjusting his tacrolimus dose. The target tacrolimus level is 10-12 ng/mL.

<table>
<thead>
<tr>
<th>Dose</th>
<th>AM administration</th>
<th>PM administration</th>
<th>Trough level</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mg BID</td>
<td>5:35 am</td>
<td>6:05pm</td>
<td>11.4 ng/mL (2-15 ng/mL)</td>
</tr>
<tr>
<td>4 mg BID</td>
<td>5:45 am</td>
<td>6:30pm</td>
<td>14.5 ng/mL (6-15 ng/mL)</td>
</tr>
</tbody>
</table>

- Keep the dose the same and recheck the level tomorrow.
- Decrease the dose to 2mg PO BID.
- Hold a dose and then decrease to 2mg PO BID.
- Increase the dose to 5mg PO BID.

Managing Drug Interactions

- DF was recently diagnosed with Aspergillus pneumonia. The infectious diseases team would like to start voriconazole 400 mg BID x 2 days followed by 200 mg BID. The team asks you how to adjust the patient's tacrolimus dose. The current dose is 6 mg PO BID.

  - Increase dose to 8 mg PO BID.
  - Monitor levels, do not dose adjust.
  - Decrease dose to 2 mg PO BID.
  - Decrease dose to 5 mg PO BID.

Dispensing Cyclosporine

- DF received a kidney transplant from his sister back in 1999. He recently moved to your neighborhood and comes to pick up his cyclosporine prescription. The prescription is written for cyclosporine 200mg PO BID. According to the orange book, what product should you dispense?

  - Apotex generic cyclosporine
  - Gengraf®
  - Sandimmune®
  - Pliva generic modified cyclosporine

MPA REM’s Pregnancy Counseling

- Which of the following is NOT an acceptable form of birth control for a woman receiving mycophenolate mofetil?

  - Mirena® (levonorgestrel-releasing intrauterine system)
  - Micette® (desogestrel/ethinyl estradiol and ethinyl estradiol) Tablets
  - Male condom and contraceptive sponge
  - NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) and a male condom
Mr. Smith is a 27 year old African American male admitted with severe nausea and vomiting. He is unable to hold down any of his immunosuppressants. The MD calls the pharmacy and asks how to administer his home regimen of tacrolimus 8 mg PO BID, mycophenolate sodium 720 mg PO BID and prednisone 20 mg PO daily.

Home regimen: Tacrolimus 4 mg PO BID, Mycophenolate sodium 720 mg PO BID and Prednisone 20 mg PO daily

- Hold immunosuppression until nausea resolves and he can tolerate oral medications
- Administer all medications intravenously at the same doses
- Administer tacrolimus at the same dose sublingually (powder from capsules), convert mycophenolate sodium to mycophenolate mofetil IV, convert prednisone 20 mg to methylprednisolone 18 mg IV
- Contact the patient’s transplant center and ask to speak with the transplant pharmacist for advice

Appropriate Regimens

Which of the following is NOT an appropriate immunosuppressive regimen?

- Belatacept + mycophenolate mofetil + prednisone
- Azathioprine + mycophenolate mofetil + prednisone
- Tacrolimus + everolimus + prednisone
- Tacrolimus + mycophenolate sodium

Key Takeaways

- Immunosuppressive regimens are individualized based on immunologic risk and medication tolerability
- Immunosuppressants are narrow therapeutic index medications that can be impacted by both drug and disease state interactions
- All New England transplant centers have an identified transplant pharmacist to assist with medication management