Transplant Clinical Pearls for the Non-Transplant Pharmacist

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Objectives

- Assess the incidence of transplantation in South Carolina and the United States
- Identify commonly used immunosuppressant medications and regimens
- Recognize and provide recommendations for commonly encountered clinical scenarios related to immunosuppressants, including:
  - Monitoring levels
  - Changing dosage formulations
  - Drug-drug interactions
  - Adverse effects

Transplant Incidence

<table>
<thead>
<tr>
<th></th>
<th>January 1, 2011 to December 31, 2011</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>South Carolina</td>
</tr>
<tr>
<td>Kidney</td>
<td>200</td>
</tr>
<tr>
<td>Liver</td>
<td>76</td>
</tr>
<tr>
<td>Kidney/Pancreas</td>
<td>18</td>
</tr>
<tr>
<td>Heart</td>
<td>24</td>
</tr>
<tr>
<td>Lung</td>
<td>5</td>
</tr>
</tbody>
</table>

Scientific Registry of Transplant Recipients. www.srtr.org

Case

DT is a 45yo AAM admitted to a General Medicine service with a 5 day history of abdominal pain, nausea, and vomiting; his last bowel movement was 6 days ago. His PMH is significant for deceased-donor kidney transplant in 2011 for ESRD secondary to HTN and DM; stable CAD; dyslipidemia; and hypothyroidism.

Home Medications:
- Tacrolimus 6 mg BID
- Mycophenolic acid 720 mg BID
- Prednisone 5 mg daily
- Amlodipine 10 mg daily
- Metoprolol 25 mg BID
- Lantus 20 units qhs
- Atorvastatin 40 mg daily
- Levothyroxine 75 mcg daily
- Aspirin 81 mg daily

Overall Goals

- Prevent acute and chronic organ rejection
- Balance risk for rejection with risk for infection/malignancy
- Minimize drug-related toxicities
Immunosuppression

<table>
<thead>
<tr>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polyclonal Antibodies</strong></td>
<td>Calcineurin Inhibitors</td>
</tr>
<tr>
<td>• Antithymocyte globulin (Thymoglobulin®, Atgam®)</td>
<td>• Cyclosporine</td>
</tr>
<tr>
<td><strong>Monoclonal Antibodies</strong></td>
<td>• Tacrolimus (Prograf®)</td>
</tr>
<tr>
<td>• Alemtuzumab (Campath®)</td>
<td><strong>Antiproliferatives</strong></td>
</tr>
<tr>
<td><strong>IL-2 Receptor Antagonists</strong></td>
<td>• Azathioprine (Imuran®)</td>
</tr>
<tr>
<td>• Basiliximab (Simulect®)</td>
<td>• Mycophenolate (CellCept®, Myfortic®)</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td><strong>mTOR Inhibitors</strong></td>
</tr>
<tr>
<td>• Methylprednisolone (SoluMedrol®)</td>
<td>• Sirolimus (Rapamune®)</td>
</tr>
<tr>
<td></td>
<td>• Everolimus (Zortress®)</td>
</tr>
</tbody>
</table>

**Case**

Abdominal X-ray showed a complete small bowel obstruction which was confirmed by CT scan. The patient is made NPO, started on maintenance fluids, and the medical resident calls you and says, “We’re holding several of his medications, I made his metoprolol and Synthroid IV, but I don’t even know what tacrolimus is—much less how to convert it to IV!”

**IV Tacrolimus**

- Risk for anaphylaxis
  - Dehydrated, hydrogenated castor oil vehicle
- Administration considerations
  - 24-hour continuous infusion
  - Dedicated peripheral line
  - Non-PVC tubing
- Increased toxicities
  - Higher concentrations
  - Nephrotoxic emulsion
  - Difficult to monitor drug levels
- Dosing
  - PO:IV dosage conversion 4:1 (or 0.03 – 0.05 mg/kg/day)
  - Max 4 mg per day

Sublingual Tacrolimus

- Alternative to IV tacrolimus
- Less toxic, less expensive
- Bypasses need for intestinal absorption
  - Rapidly absorbed through oral mucosa
  - Acceptable bioavailability shown in the literature
- Dosing & Administration
  - PO:SL dosage conversion 2:1
  - Open capsule and place powder under the tongue
  - Allow to completely dissolve before swallowing or drinking
  - Hazardous medication precautions

Case

So you have the team order:
Case

So you have the team order:

**Tacrolimus 3 mg SL BID**  
Use a gown, gloves, and mask when administering  
Open 1 capsule at a time, place contents under tongue, and  
allow to dissolve completely

When the resident tries to order DT’s mycophenolic acid, he is confused by the different options he sees in CPOE.

Case

So you have the team order:

- **Tacrolimus 3 mg SL BID**  
Use a gown, gloves, and mask when administering  
Open 1 capsule at a time, place contents under tongue, and  
allow to dissolve completely

Mycophenolate Products

- **Mycophenolate mofetil (CellCept®, MMF)**  
  Prodrug converted to active mycophenolic acid  
  Typical dose: 1000 mg PO BID  
  PO:IV dosage conversion 1:1  
  Available as a generic
- **Mycophenolic acid (Myfortic®, MPA)**  
  Enteric coated, delayed release formulation  
  Typical dose: 720 mg PO BID  
  Not available as IV formulation  
  No differences in GI side effects vs. CellCept®

CellCept® 250 mg PO = CellCept® 250 mg IV  
= Myfortic® 180 mg PO

CellCept® (mycophenolate mofetil) [package insert]  
Myfortic® (mycophenolic acid) [package insert]  

Case

You know that transplant patient’s usually have tacrolimus levels drawn. In anticipation of your team’s request, you want to know what the goal tacrolimus trough is for DT.

A. 2 to 5 ng/mL  
B. 5 to 8 ng/mL  
C. 8 to 12 ng/mL  
D. 12 to 15 ng/mL

Case

So you have the team order:

**Mycophenolate mofetil 1000 mg IV BID**

MPA 180 mg PO  
MMC 250 mg IV  

=  
MPA 720 mg PO  
MMC 1000 mg IV
Tacrolimus Monitoring

- High inter- and intra-patient pharmacokinetic variability
- 12-hour trough concentrations correlate well with AUC
- Overall goal range: 4-20 ng/mL
- Immunologic risk, time post-transplant, adverse events

### MUSC Goal Tacrolimus 12-hour Trough Concentrations Following Kidney Transplant

<table>
<thead>
<tr>
<th>Time Post-Transplant</th>
<th>Goal Trough Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1 to 6</td>
<td>8 to 12 ng/mL</td>
</tr>
<tr>
<td>Weeks 7 to 52</td>
<td>6 to 10 ng/mL</td>
</tr>
<tr>
<td>&gt; 1 year</td>
<td>&gt; 5 ng/mL, or as clinically indicated</td>
</tr>
</tbody>
</table>

Case

You know that transplant patient’s usually have tacrolimus levels drawn. In anticipation of your team’s request, you want to know what the goal tacrolimus trough is for DT.

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Case

On Hospital Day #3 DT has return of bowel function, and the team quickly advances his diet and initiates therapy with Docusate 100 mg BID, Senna 8.6 mg BID, and Polyethylene Glycol 17 g qhs to help maintain his bowel function. By Hospital Day #6, DT is tolerating a full diet complete with a small portion of meat, vegetables, a sugar-free dessert, and Fresca soda, but he has begun having multiple loose bowel movements each day, and his bowel regimen is held.

You notice that his tacrolimus trough is 16 ng/mL where as he has been well maintained with levels at the goal of 5 to 8 ng/mL throughout the hospitalization.

Key Points

- Over 300 solid organ transplants are performed each year in the state of South Carolina
- Transplant recipients are frequently admitted to non-transplant centers
- Practice caution when converting patients from PO to IV immunosuppression to ensure appropriate conversions are made
- Drug-drug and drug-food interactions are common with immunosuppressants
- Immunosuppressant goal levels are dependent on type of transplant, patient-specific risk factors, and time post-transplant
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