Kidney Transplantation: Focus on Pharmacotherapy

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Objectives

- Review immunosuppressive medications used in kidney transplantation
- Examine adverse effects, drug interactions, and monitoring parameters of these agents
- Interpret therapeutic drug monitoring for immunosuppressants
- Present “clinical pearls” related to medication usage in kidney transplant patients
IMMUNOSUPPRESSION
Goals of Immunosuppression

- Minimize Toxicity and Complications
- Prevent Rejection
Complications of Immunosuppression

- Infection

- Malignancy
  - Post-transplant lymphoproliferative disorder (PTLD)
  - Skin cancers

- Drug-specific adverse effects
Phases of Immunosuppression

- Induction
- Maintenance
- Rejection
Disclaimer: Gray Areas

- **Immunosuppressive protocols are:**
  - **Organ-specific**
    - Eg. Induction therapy is frequently used in kidney transplant but rarely in liver transplant
  - **Center-specific**
    - Eg. The regimens used for kidney transplant recipients at UCM may be different from those used at Northwestern and Rush
  - **Patient-specific**
    - Eg. If a patient develops neurotoxicity as a result of tacrolimus, may consider conversion to cyclosporine
INDUCTION
Induction

- Initiated prior to or at the time of transplantation
- Results in rapid and prolonged immunosuppression
- Goal is prevention of acute rejection in the early post-transplant period
- Use varies by transplant type and center
Agents Used in Induction

- Non-T-cell depleting
  - Interleukin-2 (IL-2) receptor antagonists
    - Basiliximab (Simulect®)
    - Daclizumab (Zenapax®)*

- T-cell depleting
  - Antithymocyte globulin
    - Rabbit (RATG, Thymoglobulin®)
    - Equine (ATG, ATGAM®)
  - Alemtuzumab (Campath®)
  - Muromomab (OKT3)*

*No longer commercially available
Basiliximab (Simulect®)

- Induction agent

- Mechanism of action: IL-2 receptor (CD25) antagonist

- Dose: 20 mg IV intraoperatively and day 4 post-transplant
  - Reduce dose to 10 mg if patient weighs <35 kg

- Adverse effects: minimal-similar to placebo
Antithymocyte Globulin

- Used for induction and treatment of rejection

- RATG more frequently selected than ATG

- Induction dose (RATG): 1.5 mg/kg IV for 3 to 7 doses
  - Usually given via a central line over 4 to 6 hours
  - Premedicate with APAP, diphenhydramine, and steroids

- Confirm that patient does not have a rabbit allergy

- Adverse effects: infusion-related reactions, leukopenia, thrombocytopenia, infection, malignancy risk
  - Dose adjustments may be needed for leukopenia/thrombocytopenia
RATG Infusion Reactions

- Symptoms: Fever, chills, labile blood pressure, muscle aches
  - Slowing infusion rate may alleviate minor reactions
  - For severe reactions: stop infusion and consider alternate therapies

- Monitoring: Vitals every 15 minutes for first hour of infusion then hourly thereafter
MAINTENANCE IMMUNOSUPPRESSION
Classes of Maintenance Immunosuppressants

- Calcineurin inhibitors (CNIs)
- Antiproliferatives
- Corticosteroids
- mTOR (signal proliferation) inhibitors
- Co-stimulation blocker
**Maintenance Immunosuppression**

- Typically consists of two to three medications from **different** classes
  - CNI + antiproliferative +/- steroids
  - mTOR inhibitor + CNI + steroids
  - mTOR inhibitor + antiproliferative + steroids
  - Co-stimulation blocker + antiproliferative + steroids

- Regimen may be minimized over time

- Note that immunosuppressants are frequently used off-label
Calcineurin Inhibitors (CNIs)

- Cyclosporine (CSA)
- Tacrolimus (TAC, AKA: FK506)

- Mechanism of action: Decrease production of interleukin (IL)-2 and other cytokines to inhibit T cell proliferation
  - Cyclosporine binds to cyclophilin
  - Tacrolimus binds to FK-binding protein

- Pharmacokinetics: CYP3A4 and P-glycoprotein substrates (=LOTS of drug interactions)
**Tacrolimus (Prograf®, Envarsus XR®, Astagraf XL®)**

- **Most commonly used CNI**
  - Considered more potent than CSA and has largely replaced it in the market

- **Usual dose**
  - Initial: Patient-specific, typical starting dose is 0.05 mg/kg PO every 12 hours (immediate-release tacrolimus)
  - May delay initiation in the short term post-transplant
  - Titrated to desired goal trough range (eg. 4-12 ng/mL)

- **Routes of administration**
  - PO: capsules (Prograf/Astagraf 0.5 mg, 1 mg, 5 mg capsules, Envarsus 0.75 mg, 1 mg, 4 mg tablets), suspension (compounded)
  - Sublingual: open capsules and sprinkle contents under tongue
  - IV: **AVOID** if possible
Tacrolimus

- Adverse effects
  - Nephrotoxicity
  - Electrolyte abnormalities (hyperkalemia, hypomagnesemia)
  - Hypertension
  - Hyperlipidemia
  - Post-transplant diabetes
  - Neurotoxicity
  - Alopecia
Cyclosporine (CSA)

- First CNI developed

- Usual dose
  - Initial: patient-specific, typically ~3 mg/kg PO every 12 hours
  - May delay initiation in the short term post-transplant
  - Adjusted to achieve desired goal trough range (eg. 100-300 ng/mL)

- Routes of Administration
  - PO: capsules (25 mg, 100 mg), solution
  - IV: AVOID if possible
Cyclosporine

- Adverse effects
  - Nephrotoxicity
  - Electrolyte abnormalities (hyperkalemia, hypomagnesemia)
  - **Hypertension**
  - Hyperlipidemia
  - Post-transplant diabetes
  - Neurotoxicity
  - **Hirsutism**
  - **Gingival hyperplasia**
Cyclosporine Products

- Cyclosporine (Non-Modified)
  - Sandimmune®
  - Cyclosporine USP

- Cyclosporine Modified
  - Neoral®
  - Gengraf® (branded generic)
  - Cyclosporine Modified USP

**REMEMBER:**
- Sandimmune® ≠ Neoral®
- Cyclosporine ≠ Cyclosporine Modified
# CNIs: CYP3A4 and P-glycoprotein Drug Interactions

<table>
<thead>
<tr>
<th>Drugs that <strong>DECREASE</strong> blood levels of CNIs</th>
<th>Drugs that <strong>INCREASE</strong> blood levels of CNIs</th>
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<tbody>
<tr>
<td>Anticonvulsants:</td>
<td>Calcium Channel Blockers:</td>
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<tr>
<td>Carbamazepine</td>
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<td>Phenytoin</td>
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<td>Antimicrobials:</td>
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<td>Macrolides:</td>
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<td>Clarithromycin</td>
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<td>St. John’s Wort</td>
<td>Erythromycin</td>
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<td>Antiretrovirals:</td>
<td>Others:</td>
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<tr>
<td>Efavirenz</td>
<td>Amiodarone</td>
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<tr>
<td>Efavirenz</td>
<td>Protease inhibitors</td>
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</tbody>
</table>
CNIs: Interactions

- **Drug-Disease State Interactions**
  - QTc prolongation (especially with TAC)
  - Diarrhea (increases TAC exposure)
  - Liver dysfunction

- **Drug-Food Interactions**
  - Grapefruit and grapefruit juice (CYP3A4 inhibitor)
CNI-Induced Nephrotoxicity

- **Acute**
  - Hemodynamically-mediated nephropathy
  - Often exposure-dependent
  - Signs and symptoms include ↑SCR, ↑BP, ↑K—may resemble acute rejection

- **Chronic**
  - May result in irreversible kidney damage
CNIs-Therapeutic Drug Monitoring (TDM)

- Important for evaluating efficacy and toxicity

- 12 hour trough levels are use for immediate-release TAC and CSA, 24 hour troughs for extended-release TAC

- Half-life
  - Tacrolimus ~11 hours
  - Cyclosporine ~19 hours

- Time to achieve steady state ~3-5 half-lives
CNIs-Therapeutic Drug Monitoring (TDM)

- When assessing levels, the following should be taken into consideration:
  - Is it a “true” trough?
  - Goal range (may be per protocol or patient-specific)
  - Serum creatinine trend
  - Previous drug levels (does this level “make sense?”)
  - CNI dose
  - Concomitant medications
    - Prescription, OTC, and herbals
    - New/recently discontinued medications
  - Any complaints of side effects? Evidence of graft dysfunction?
  - Other factors: adherence, diarrhea, drug-food interactions
Antiproliferatives

- Mycophenolate products
  - Mycophenolate mofetil (Cellcept®)
  - Mycophenolate sodium (Myfortic®)

- Azathioprine (Imuran®)
  - Largely replaced by mycophenolate
  - May still be preferred agent in select situations
    - GI intolerance to mycophenolate
    - Females who are trying to get pregnant
Mycophenolate Products

- Mycophenolate mofetil (MMF)
  - Brand name: Cellcept®

- Mycophenolate sodium (EC-MPS)
  - Brand name: Myfortic®

- Mechanism of action: Depletes guanosine halting progression of activated T and B lymphocytes during S phase
MPA Metabolism

MMF or EC-
MPS

Minor

MPA

Minor

7-0-Glucoside

EHC

(Enterohepatic Cycling)

MPAG

Acyl
Glucuronide
Mycophenolate Mofetil (Cellcept®)

- Usual dose: 1000 mg PO twice daily

- Adverse effects: GI problems (diarrhea, nausea, vomiting, abdominal pain), leukopenia

- Drug interactions
  - Divalent/trivalent cations (Ca, Mg, Iron)
  - CSA (decreased AUC)
  - Bile acid sequestrants (decreased AUC)

- Routes of administration
  - PO: capsules (250 mg), tablets (500 mg), suspension
  - IV: Note that PO:IV conversion is 1:1
Mycophenolate Sodium (Myfortic®)

- Enteric-coated formulation
  - Proposed benefit is reduced incidence of GI toxicity

- Usual dose: 720 mg PO BID
  - Available as 180 and 360 mg tablets

- Conversions between products
  - MMF:EC-MPS
    - Eg. Cellcept® 1000 mg PO BID=Myfortic® 720 mg PO BID
CSA/MPA Drug Interaction

MMF or EC-MPS

→ MPA

↓ Minor

7-0-Glucoside

(Enterohepatic Cycling)

Acyl Glucuronide

↓ CSA inhibits EHC; ↓MPA, ↑MPAG

Minor

MPAG
Effect of EHC/CSA on MPA

- **Dose**
- **Time (h)**
- **MPA Concentration (ng/mL)**
- **Trough (C₀)**
- **C_pmax**
- **TAC**
- **Second Peak (EHC)**
- **Trough (C₀)**
- **CSA**

The graph illustrates the effect of EHC/CSA on MPA concentration over time. Key points include:

- **TAC** (Time Averaged Concentration)
- **C_pmax** (Peak Concentration)
- **Second Peak (EHC) and CSA**

The graph shows the concentration of MPA at different times, with distinct markers indicating peak and trough concentrations under the influence of EHC/CSA.
Mycophenolate Products: TDM

- Controversial-dose adjustments typically related to patient’s ability to tolerate medications
  - 12-hour trough levels
    - May relate to toxicity and adherence

- Mini-AUC
  - May relate to efficacy
  - If on tacrolimus:
    - MPA trough level, 30 minutes, and 2 hours post-dose
  - If cyclosporine:
    - MPA trough level, 2 hours, 3 hours, and 4 hours post-dose
  - Cannot be performed accurately if patient on mycophenolate sodium due to delayed drug release
Mycophenolate REMS

- Education for women of child-bearing potential and their providers
- Encourages appropriate forms of birth control
- Reporting pregnancies that occur to national registry
Azathioprine (Imuran®)

- Mechanism of action: Inhibits inosinic acid monophosphate dehydrogenase (IMPDH) and therefore DNA replication in rapidly dividing cells

- Usual dose
  - 1-2 mg/kg/day common maintenance dose

- Adverse effects: myelosuppression, hepatitis, cholestasis, pancreatitis
Azathioprine (Imuran®)

- Drug interactions: xanthine oxidase inhibitors, warfarin (decreases its anticoagulant effect)

- Routes of administration:
  - PO: tablets (50 mg)
  - IV: currently on drug shortage

- TDM
  - No routine drug level monitoring, consider checking 6-thioguanine levels if concerns about toxicity
Azathioprine-Xanthine Oxidase Inhibitors

- Avoid concomitant use with allopurinol and febuxostat
  - Xanthine oxidase is responsible for metabolism of azathioprine -> inhibition of this enzyme -> increased exposure to 6-MP -> hematologic toxicity
  - Consider switch to alternative antiproliferative agent if xanthine oxidase inhibitor absolutely necessary
Leflunomide (Arava®)

- May be selected as a replacement antiproliferative in patients with concomitant viral infections (eg. BK, CMV)

- Typical dose: 40 mg PO daily (our practice is to avoid load due to tolerability issues), does have extremely long half-life

- Adverse effects: rash, hepatotoxicity, neuropathy

- Teratogenic
Corticosteroids

- Prednisone (PO) or methylprednisolone (IV)

- Mechanisms of action: Prevent the expression of genes encoding cytokines, inhibit production of IL-2

- Usual dose and/or use varies by transplant center protocol
  - Steroid avoidance, rapid taper, and minimization protocols may be utilized
Corticosteroids

- Steroids (if used) are generally tapered over a period of weeks, most patients ultimately end up on ~5 mg/day

- Oral to IV conversion
  - Prednisone: Methylprednisolone ratio of 5:4
    - Prednisone 20 mg PO daily ➔ Methylprednisolone 16 mg IV daily
Sirolimus (Rapamune®)

- Mechanism of action: Inhibits mammalian target of rapamycin (mTOR) – blocking intracellular signals past IL-2 receptor

- Initially studied for use with CSA in kidney transplant
  - Now often utilized in place of a CNI or antiproliferative
Sirolimus (Rapamune®)

- **Usual dose**
  - 1-5 mg PO daily
  - Avoid “loading” doses due to tolerability

- **Drug interactions**
  - CYP3A4
  - Administer at least 4 hours after CSA if used together
Sirolimus (Rapamune®)

- Adverse effects:
  - Hyperlipidemia
  - Leukopenia
  - Thrombocytopenia
  - Edema
  - Proteinuria
  - Interstitial pneumonitis
  - Mouth ulcers
  - Delayed wound healing
Sirolimus (Rapamune®)

Role in transplant
- Infrequently used immediately post-transplant due to wound healing complications
- “Renal sparing” protocols
- Beneficial in patients with malignancies (specifically skin cancers)
Everolimus (Zortress®)

- Initial dose: 0.75 mg PO twice daily
- Adverse effects: similar to sirolimus
- Drug interactions: similar to sirolimus, exception—does not need to be separated by 4 hours from CSA
mTOR Inhibitors: TDM

- **Sirolimus**
  - 24 hour trough
  - Goal range varies, typically 4-7 ng/mL
  - Note long half life (57-63 hours)->takes significant time to reach steady state

- **Everolimus**
  - 12 hour trough
  - Goal range=3-8 ng/mL
  - Half-life=30 hours
Belatacept (Nulojix®)

- Mechanism of action: selective T cell co-stimulation blocker

- First **IV-only** agent for maintenance immunosuppression

- Approved for use in kidney transplant in combination with mycophenolate, corticosteroids, and basiliximab induction
Belatacept (Nulojix®)

- **Dose:** fixed dose based on weight
  - **Initial immunosuppression:** 10 mg/kg IV on POD 0, POD 4, end of week 2, week 4, week 8, and week 12, 5 mg/kg IV end of week 16, and monthly thereafter
  - **Conversion:** 5 mg/kg IV every 2 weeks for 5 doses, then every 4 weeks thereafter

- **Administration:** IVPB over 30 minutes, can be given peripherally

- **Common adverse effects:** anemia, diarrhea, UTI, peripheral edema
Belatacept: Black Box Warnings

- Post-transplant lymphoproliferative disorder (PTLD)
  - Use limited to **Epstein-Barr virus (EBV) positive** recipients only

- Progressive multifocal leukoencephalopathy (PML)

- Requires registration for drug access via Nulojix Distribution Program
Belatacept (Nulojix®)

- Potential role in transplant
  - Not nephrotoxic
  - Decreased cardiovascular and metabolic side effects compared to CNIs
  - IV-only administration allows for direct assessment of compliance
  - Doesn’t require drug level monitoring
  - No known drug interactions
Pharmacokinetic Drug Interactions - Management

- For the majority of medications, CNI/mTOR inhibitor doses are not empirically reduced, rather tend to follow drug levels and adjust as necessary
  - Depends on patient’s clinical status and history

- If an interacting medication is started or stopped, recommend checking trough levels

- When in doubt, look it up or consult a transplant pharmacist!
Pharmacokinetic Drug Interactions

- CYP 450 enzyme INDUCERS

- Increase drug metabolism, potentially resulting in decreased efficacy

- Examples:
  - Anti-epileptics (eg. phenytoin, carbamazepine)
  - Antibiotics (eg. rifampin)
  - Antiretrovirals (eg. efavirenz)
  - Herbals (eg. St. John’s wort)
Pharmacokinetic Drug Interactions

- CYP 450 enzyme INHIBITORS

- Decrease drug metabolism, potentially resulting in toxicity

- Examples:
  - Antifungals: azoles
  - Antibiotics: macrolides
  - Antiretrovirals: protease inhibitors
  - Hepatitis C medications: telaprevir, boceprevir
  - Cardiac meds: eg. verapamil, diltiazem, amiodarone
Pharmacodynamic Drug Interactions

- ACE inhibitors/ARBs
- NSAIDs
- Nephrotoxic drugs (additive toxicity)
- Myelosuppressive drugs (additive toxicity)
FAQ:

AM meds “held for dialysis”
Pearl:
Dialysis and Immunosuppressants

- **Induction:**
  - OK to hold if needed
  - Not removed by dialysis, but ideal to avoid problem of differentiating Thymo infusion-related reaction from dialysis tolerance

- **Maintenance:**
  - Do **NOT** hold tacrolimus, cyclosporine, mycophenolate, everolimus, sirolimus, steroids
  - **DO** hold azathioprine until after HD
  - **DO** hold meds for infectious ppx until after HD
FAQ:

Can I give Thymoglobulin through a peripheral line?
Pearl:
Peripheral Thymoglobulin

- Doses prepared for central administration (eg. 0.5 mg/mL concentration) CANNOT be given through a peripheral line
- For peripheral administration, doses must be:
  1. Diluted to a max of 0.25 mg/ml (not 0.5 mg/mL) AND
  2. Infused over at least 12 hours (not 6 hours)
- Phlebitis and thrombophlebitis are concerns! If this occurs, stop the infusion and contact the transplant pharmacist to arrange a bag with heparin and hydrocortisone mixed in.
FAQ:
My patient can’t swallow.
Can I crush or dissolve his meds?
Change to IV?
<table>
<thead>
<tr>
<th>Medicine</th>
<th>PO</th>
<th>NG</th>
<th>SL</th>
<th>IV</th>
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</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>Possible but NG preferred PO:IV 5:1</td>
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<tr>
<td>Tacrolimus, extended release</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Envarsus XR on formulary, Astagraf XL removed from formulary</td>
<td>No; consider tacrolimus</td>
<td></td>
<td></td>
<td>No; consider tacrolimus</td>
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<tr>
<td>Cyclosporine, modified</td>
<td>✔</td>
<td>✔</td>
<td>Must use liquid</td>
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<tr>
<td>Nonformulary; use patient’s own or cyclosporine modified</td>
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<td></td>
<td></td>
<td>No; use cyclosporine, nonmodified</td>
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<tr>
<td>Cyclosporine, nonmodified</td>
<td>✔</td>
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<td>Must use liquid</td>
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<tr>
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<td>Possible but NG preferred PO:IV 3:1</td>
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<tr>
<td>Mycophenolate mofetil (MMF)</td>
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<td>Mycophenolic acid (MPA)</td>
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<tr>
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<td>Prednisone</td>
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</tbody>
</table>

**Notes:**
- PO:SL 1:0.5-1
- MPA:MMF 720:1000
Kidney Transplantation: Focus on Pharmacotherapy

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