An Overview of Pharmacokinetic of Cyclosporin A, Tacrolimus and Sirolimus

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Maintenance Pharmacotherapy

- Calcineurin Inhibitors
  - Cyclosporine
  - Tacrolimus
- Antiproliferative
  - Azathioprine
  - Mycophenolate Mofetil
  - Cyclophosphamide
  - Methotrexate
- Corticosteroids
- Sirolimus
Summary of Immunosuppressant Pharmacology

<table>
<thead>
<tr>
<th></th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
<th>Sirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding Protein</td>
<td>Cyclophilin</td>
<td>FKBP</td>
<td>FKBP</td>
</tr>
<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>G0-G1</td>
<td>G0-G1</td>
<td>G1-S</td>
</tr>
</tbody>
</table>
Pharmacokinetics:
Cyclosporine, Tacrolimus and Sirolimus

- High Variable Drug
- Metabolized via Liver - CYA 3A4
- P-Glycoprotein Substrate/Inhibitor
Is there a Relationship Between Dose, Blood Levels and Efficacy/Toxicity?
Highly Variable Drugs

1. AUC
2. Cmax
3. Tmax
Highly Variable Drugs

Extent and rate of absorption are highly variable. Patient differences are highlighted in the absorption phase.

Adapted from Johnston A et al. *Transplant Proc.* 2000;32:53S-56S.
Blood Concentration

Toxicity

Rejection
# Management During Maintenance Phase

<table>
<thead>
<tr>
<th>Therapeutic</th>
<th>Infections</th>
<th>Malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>Nephrotoxicity</td>
<td>30-40%</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>30-55%</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>5-10%</td>
</tr>
<tr>
<td></td>
<td>Neurotoxicities</td>
<td>10-30%</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>Breakthrough Rejection</td>
<td></td>
</tr>
</tbody>
</table>
Toxicity No Effect
Oops! Too Much Too Little
↓ Dose ↑ Dose
No effect
→ Too Little ↑ Dose
→ No Effect
→ Too Much ↓ Dose
→ Toxicity ↓ Dose
Initiation and Management of Drug Therapy

Therapeutic objective (prevention of rejection)

Choose drug & dosing regimen (CSA BID)

Monitor therapeutic and toxic response (CSA level and NTX)

PK

PD
Background

- **Three main categories of TDM**
  - Pharmacogenomics
  - Pharmacokinetic
  - Pharmacodynamic

- **TDM can be affected by**
  - Disease states
  - Laboratory results
  - TDM & wallet
Therapeutic Drug Monitoring

**Cyclosporine**

- **Timing**
  - Trough
  - 2 and 12 hour post-dose level
  - Sparse sample AUC
  - Complete Area Under the Curve
- **Type**
  - Plasma vs. whole blood
  - Monoclonal vs Polyclonal
  - RIA, FPIA, HPLC, EMIT
Target Cyclosporine Blood Concentration

Adapted from Johnston A et al. *Transplant Proc.* 2000;32:53S-56S.
Guidelines for Cyclosporine Target $C_2$ Levels

<table>
<thead>
<tr>
<th>Transplant</th>
<th>Time post-transplant (months)</th>
<th>Target $C_2$ concentration (µg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>1</td>
<td>1’700</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1’500</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1’300</td>
</tr>
<tr>
<td></td>
<td>4–6</td>
<td>1’100</td>
</tr>
<tr>
<td></td>
<td>7–12</td>
<td>900</td>
</tr>
<tr>
<td></td>
<td>&gt; 12</td>
<td>800</td>
</tr>
<tr>
<td>Liver</td>
<td>0–3</td>
<td>1’000</td>
</tr>
<tr>
<td></td>
<td>4–6</td>
<td>800</td>
</tr>
<tr>
<td></td>
<td>&gt; 6</td>
<td>600</td>
</tr>
</tbody>
</table>
Cyclosporine

- Pharmacokinetics
  - Distribution
    - 50-60% erythrocyte accumulation
    - 10-20% leukocyte accumulation
  - Metabolism - hepatic
    - Cytochrome P-450 3A4, P-glycoprotein
    - Metabolites
  - Excretion
    - Biliary
    - 6% excreted in the urine
Cyclosporine

Dosing

- Factors
  - Clinical status of patient
  - Formulation, additional drugs

- Range
  - Initial: 8-10 mg/kg/day
  - Late: 3-5 mg/kg/day
Cyclosporine

- Adverse Reactions
  - Hypertension
  - Nephrotoxicity
  - CNS manifestations
  - Hyperglycemia
  - Hyperlipidemia
  - Dermatologic manifestations
  - Electrolyte abnormalities
### CYP3A4

<table>
<thead>
<tr>
<th><strong>Substrate</strong></th>
<th><strong>Inhibitors</strong></th>
<th><strong>Inducers</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine, FK506</td>
<td>Erythromycin</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Clarithromycin</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Diltiazem</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Felodipine, isradipine</td>
<td>Ketoconazole</td>
<td>Rifabutin</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Fluconazole</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>Itraconazole</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>Quinidine</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Digoxin, quinidine</td>
<td>Grapefruit juice</td>
<td>Troglitazone</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Cimetidine</td>
<td>St. John’s wort</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Indinavir</td>
<td></td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Fluoxetine</td>
<td></td>
</tr>
<tr>
<td>Astemizole</td>
<td>Zileuton, Zafirlukast</td>
<td></td>
</tr>
<tr>
<td>Terfenadine</td>
<td>Verapamil</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Amiodarone</td>
<td></td>
</tr>
</tbody>
</table>
Cyclosporine

- Pharmacodynamic Drug Interactions
  - Nephrotoxicity
    - Amphotericin
    - NSAIDS
    - Aminoglycosides
    - Tacrolimus
Cyclosporine

Pharmacodynamic Drug Interactions

- Gingival Hyperplasia
  - Nifedipine, Phenytoin

- Hirsutism
  - Phenytoin, Prednisone

- Rhabdomyolysis, Myositis
  - Statins, Colchicine
We Must Remember That the Absence of Evidence Is Not the Evidence of Absence
Anticonvulsants and Allograft Survival

n=20 Hx of Seizure and n=92 control

Wassner et. J of Ped 1976;88:134
Pharmacogenomics;
Going Down the Rabbit Hole
Variability in Response to Drug Therapy

Pharmacogenomics
Study of variability in drug response determined by multiple genes within the genome
Genetically Based Optimization of Drug Dosing

Responders
Non-responders
Toxic responders
African American vs Caucasian Cyclosporine

Lee M et al. *Journal of Clinical Pharmacology, 2001;41:317-323*
Pharmacogenetics

Thiopurine N-methyl transferase (TPMT)

Allele frequency in Caucasians

- **89%**: Homozygous for TPMT wild type — High TPMT activity
- **10%**: Heterozygous for one non-functional allele — Intermediate TPMT activity
- **0.5-1%**: Homozygous for two non-functional alleles — Low TPMT activity
Tacrolimus (FK-506)

- Mechanism of Action
  - Binds to FK binding protein-12 (FKBP-12)
  - Complex then inhibits activity of calcineurin
  - Inhibits early phase T-cell activation
  - Inhibits gene encoding IL-2
  - Does not inhibit late-phase of T-cell activation
Tacrolimus

- **Absorption**
  - Range 5-67% (mean of 29%)
  - Extent, rate reduced by food (fat content)
  - Not bile dependent

- **Distribution**
  - Partitions into erythrocytes
    - Blood : plasma ratio variable
  - Present in placenta, fetal circulation, breast milk
Tacrolimus

- **Metabolism**
  - Hepatically metabolized
    - Impaired liver function reduces clearance
  - Cytochrome P450-3A4 isoenzyme
    - Intestinal metabolism may affect bioavailability
  - Pediatric patients have higher clearance
    - Dose (mg/kg) greater than adults
Tacrolimus

- Excretion
  - Less than 1% eliminated in urine
Tacrolimus

- **Dosing**
  - 0.15 mg/kg q12h
  - In OHSU; 0.1 mg/kg/day
    - Higher dose may be required in African-Americans

- **Therapeutic Drug Monitoring**
  - 0.5-1.5 ng/mL (plasma)
  - 5-15 ng/mL (whole blood)
Tacrolimus

- Adverse Effects
  - Hypertension
  - Hyperlipidemia
  - Nephrotoxicity
  - Hyperglycemia
  - Electrolyte abnormalities
  - CNS manifestations
Tacrolimus

- Drug Interactions - similar to CYA

- Monitoring Parameters - similar to CYA
  - Diabetogenic
  - CNS toxicity
African American vs Caucasian Tacrolimus

27 kidney Tx patients
7 black
16 Caucasian
4 Asian
Tacrolimus dose over 3 months > 0.28mg/kg
6/7 blacks
2/20 Caucasian and Asian

Dose of Tacrolimus

<table>
<thead>
<tr>
<th>Condition</th>
<th>Tacrolimus</th>
<th>CYA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>54.1%</td>
<td>33.8%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19.9%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>7.8%</td>
<td>14.5%</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>0.5%</td>
<td>8.7%</td>
</tr>
</tbody>
</table>
MPA AUC to Trough Correlation

Sievers, et al. Presented at ATC, Seattle, WA 2005

Incidence of Acute Rejection Associated With MMF in African American Patients

BPR/TF = biopsy-proven rejection/treatment failure.
Patients also received cyclosporine plus corticosteroids plus antithymocyte globulin induction therapy.

US and Global Sirolimus Trials: GFR (ml/min) at 12 months

US Study
- AZA: 66
- Srl 2 mg: 57
- Srl 5 mg: 55

Global Study
- AZA: 62
- Srl 2 mg: 55
- Srl 5 mg: 53
Pharmacodynamic Drug Interactions
(CSA and Sirolimus)

Sirolimus in Combination with Tacrolimus Is Associated with Worse Renal Allograft Survival

Log-Rank p-value < .001
* TAC = Tacrolimus, SRL = Sirolimus, MMF = Mycophenolate Mofetil
Sirolimus

* Mechanism
  * Binds to FKBP-12
  * Does not inhibit calcineurin
  * Inhibits IL-2 stimulated proliferation of T-cells
  * Synergistic with CSA
Sirolimus

- Pharmacokinetics
  - Low oral bioavailability
  - Extensive blood : plasma partitioning
  - Half life = 60 hours
  - Metabolized by the cytochrome P450-3A4
Sirolimus

- Therapeutic Drug Monitoring
  - Pharmacokinetic
  - Pharmacodynamic
    - P70 S6 kinase assay
Sirolimus

- **Benefits**
  - Less nephrotoxicity
  - Less effect on blood pressure
  - Lack of increased rate of infection

- **Side Effects**
  - Dose dependent thrombocytopenia
  - Hyperlipidemia
What is a biomarker?

- Alternatively:
  - “A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic response(s) to a therapeutic intervention”

Biomarkers in Transplant Management

![Box plot showing biomarker values for different conditions](image)

- FDA Trial Healthy (n = 155)
- Rejection (n = 39)
- Stable (n = 504)
- Infection (n = 66)

Values:
- 415
- 488
- 249
- 111

Significance levels:
- P < 0.001

Legend:
- Strong
- Moderate
- Low
Relative Risk of Rejection and Infection Correlates with Immune Function
Lack of correlation between ATP immune response and tacrolimus levels.
Pharmaceutical Equivalents

Drug products are considered pharmaceutical equivalents when both agents contain identical amounts of active ingredients in the same salt or ester form, dosage form, route of administration, and possess identical disintegration times and dissolution rates.

Federal Register 1997
Therapeutic Equivalents

Drug products are considered therapeutically equivalent when the generic drugs are pharmaceutical equivalents and show the same efficacy and safety profile as that product whose efficacy and safety has been established.

Federal Register 1997
Bioequivalence

Bioequivalency is defined as pharmaceutical equivalents that display the same rate and extent of absorption.

Biologic equivalence means therefore, delivering the same amount of active drug moiety to the site of action when a generic drug and innovator drugs are administered at the same molar dose under similar conditions.

Federal Register 1997
What Criteria Must Be Met for EXPECTED same Clinical Effect?

- Meet compendial standards
- Meet Appropriate bioequivalence standard
- Meet GMP (Good Manufacturing Practice) Standard
Standard Bioequivalence Study

- Cross-over (n=24-36 patients)
- Single dose of test and reference products
- Measurement
  - AUC and Cmax
- Statistical Criteria:
  - If two formulation’s rate and extent of absorption differ only by -20%/+25% or less
Why are Physicians and Patients Suspicious of Generic Drugs

- They have never been provided information that validates the arbitrary bioequivalence requirement
Evaluation of 224 ANDA Drug Products

Mean Diff. in AUC generic vs innovator: 3.5%

Percentage of Products within ±5% of innovator AUC: 80%

Percentage of Products having greater than 15% difference from innovator AUC: 0.43% (1 product)

Nightingale and Morrison JAMA 1987:258;1200
# Model for Generic Drugs

## Days Post-Transplantation (Less than 6 months)

<table>
<thead>
<tr>
<th>Dose* (day)</th>
<th>500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of active CSA absorbed (30%)</td>
<td>150 mg</td>
</tr>
<tr>
<td>Amount of active CSA absorbed (50%)</td>
<td>250 mg</td>
</tr>
<tr>
<td>Incremental difference in bioavailability</td>
<td>±10%</td>
</tr>
<tr>
<td>Max. change in mg of cyclosporine</td>
<td>±50 mg/day</td>
</tr>
<tr>
<td>Max. mg of cyclosporine absorbed (30%)</td>
<td>±15 mg/day</td>
</tr>
<tr>
<td>Max. mg of cyclosporine absorbed (50%)</td>
<td>±25 mg/day</td>
</tr>
</tbody>
</table>

* CSA dose: 7 mg/kg/day
# Model for Generic Drugs

## Days Post-Transplantation (greater than 6 months)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong> <em>(day)</em></td>
<td>250 mg</td>
</tr>
<tr>
<td><strong>Amount of active CSA absorbed (30%)</strong></td>
<td>75 mg</td>
</tr>
<tr>
<td><strong>Amount of active CSA absorbed (50%)</strong></td>
<td>125 mg</td>
</tr>
<tr>
<td><strong>Incremental difference in bioavailability</strong></td>
<td>± 10%</td>
</tr>
<tr>
<td><strong>Max. change in mg of cyclosporine</strong></td>
<td>±25 mg/day</td>
</tr>
<tr>
<td><strong>Max. milligram of CSA absorbed (30%)</strong></td>
<td>±7.5 mg/day</td>
</tr>
<tr>
<td><strong>Max. milligram of CSA absorbed (50%)</strong></td>
<td>±12.5 mg/day</td>
</tr>
</tbody>
</table>

* CSA dose: 4 mg/kg/day
Percentage of Patients with Trough Cyclosporine (Neoral) Levels Within, Above or Below the Desired Range

- Below Range
- Above Range
- Within Range

International Sandimmune Neoral Study Group
Frei UA, Transplantation 1998;65:1455
## Cost of Immunosuppressive Drugs

<table>
<thead>
<tr>
<th>Acquisition Cost</th>
<th>AWP</th>
<th>Non-profit Pharmacy</th>
<th>For-profit Pharmacy</th>
<th>MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoral 25 mg</td>
<td>1.44</td>
<td>60%</td>
<td>82%</td>
<td>1.41</td>
</tr>
<tr>
<td>Sandimmune 25 mg</td>
<td>1.61</td>
<td>58%</td>
<td>81%</td>
<td>1.41</td>
</tr>
<tr>
<td>Neoral 100 mg</td>
<td>5.77</td>
<td>65%</td>
<td>82%</td>
<td>5.69</td>
</tr>
<tr>
<td>Sandimmune 100 mg</td>
<td>6.40</td>
<td>55%</td>
<td>80%</td>
<td>5.69</td>
</tr>
</tbody>
</table>

AWP: Average Wholesale Price  
MAC: Maximum Allowable Cost
## Cost of Immunosuppressive Drugs

<table>
<thead>
<tr>
<th>Acquisition Cost</th>
<th>Non-profit Pharmacy ($)</th>
<th>70 Kg Pt. (daily cost $)</th>
<th>70 Kg Pt. (yearly cost $)</th>
<th>Cost saving ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic CSA at 75% of AWP</td>
<td>4.32</td>
<td>12.96</td>
<td>4,730</td>
<td>- 613</td>
</tr>
<tr>
<td>Generic CSA at 50% of AWP</td>
<td>2.88</td>
<td>8.64</td>
<td>3,157</td>
<td>960</td>
</tr>
<tr>
<td>Cost of TDM ($)</td>
<td>70</td>
<td></td>
<td></td>
<td>???</td>
</tr>
</tbody>
</table>
Target Cyclosporine Blood Concentration

Toxicity

Rejection
## Bioequivalence and Drug Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Outcomes</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Intoxication</td>
<td>BMJ 1971;2:271</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Lack of effect</td>
<td>Am J Psych 1979;136:4 A</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Lack of effect</td>
<td>Lancet 1987;1:1432</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Rejection</td>
<td>Drug Safety 1994;11:1</td>
</tr>
</tbody>
</table>
Are Generic Drugs Less Expensive?

Always buying generic drug will save the consumer money

Always seeking and buying the least expensive, whether generic or brand drug will save the consumer even more money
On some positions, cowardice asks the question, is it expedient? And then expedience comes along and asks the question - is it political? Vanity asks the question - is it popular? Conscience asks the question is it right? And there comes a time when one must take a position that is neither safe, nor political, nor popular - but one must take it because it’s right.

Martin Luther King, Jr., 1968
Growing old is mandatory, growing wise is optional