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 Immunosuppresant Pharmacology

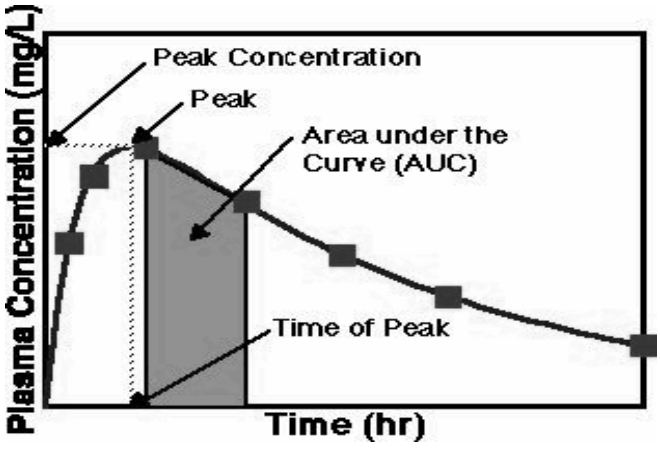
	Cyclosporine	Tacrolimus	Sirolimus
Binding Protein	Cyclophilin	FKBP	FKBP
Effector Protein	Calcineurin	Calcineurin	mTOR
IL-2 Message	Inhibited	Inhibited	_____
IL-2 Response	_____	_____	Inhibited
Cell Cycle Effect	G0-G1	G0-G1	G1-S

Pharmacokinetics: Cyclosporine, Tacrolimus and Sirolimus

- High Variable Drug
- Metabolized via Liver - CYA 3A4
- P-Glycoprotein Substrate/Inhibitor

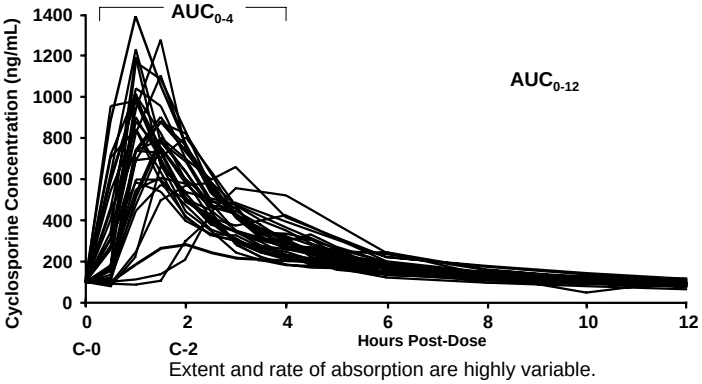
Is there a Relationship Between Dose, Blood Levels and Efficacy/Toxicity?

Highly Variable Drugs



1. AUC
2. Cmax
3. Tmax

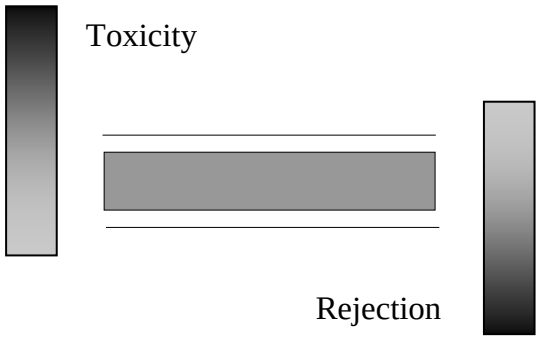
Highly Variable Drugs



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

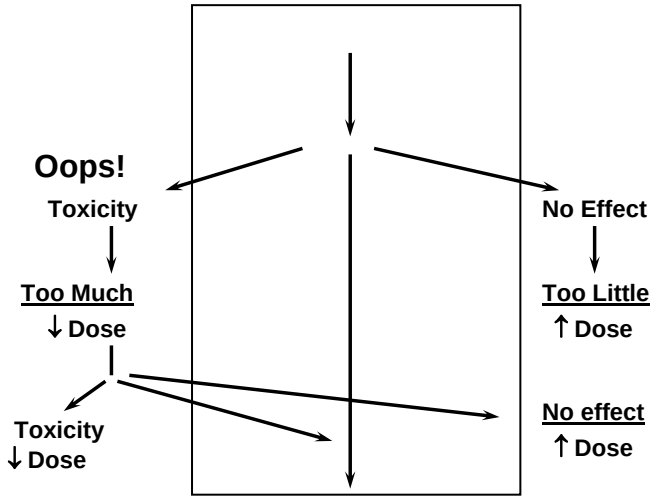
Adapted from Johnston A et al. *Transplant Proc.* 2000;32:53S-56S.

Blood Concentration

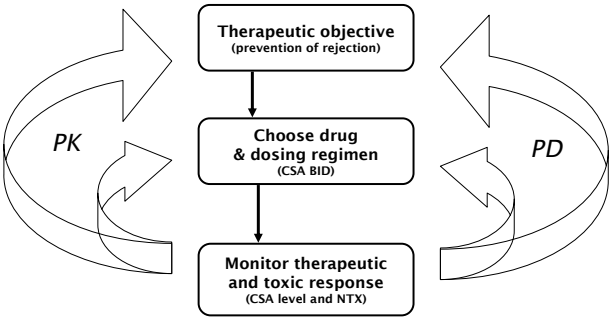


Management During Maintenance Phase

	Infections	Malignancies
High		
Therapeutic	Nephrotoxicity Hypertension Diabetes Neurotoxicities	30-40% 30-55% 5-10% 10-30%
Low	Breakthrough Rejection	



Initiation and Management of Drug Therapy



Background

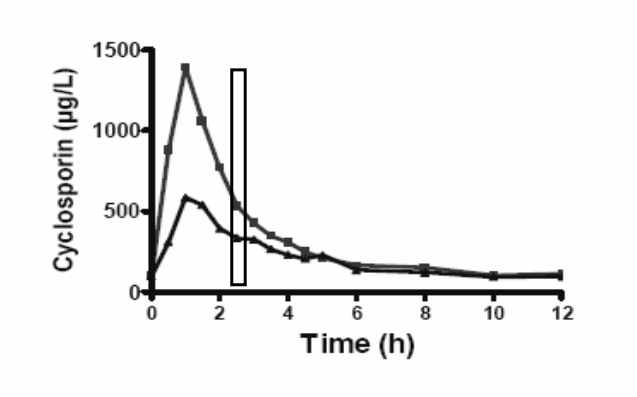
- **Three main categories of TDM**
  - Pharmacogenomics
  - Pharmacokinetic
  - Pharmacodynamic
- **TDM can be affected by**
  - Disease states
  - Laboratory results
  - TDM & wallet

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

Transplant	Time post-transplant (months)	Target C_2 concentration (µg/l)
Renal	1	1'700
	2	1'500
	3	1'300
	4–6	1'100
	7–12	900
	>12	800
Liver	0–3	1'000
	4–6	800
	>6	600

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

Substrate	Inhibitors	Inducers
Cyclosporine, FK506	Erythromycin	Carbamazipine
Corticosteroids	Clarithromycin	Phenobarbital
Erythromycin	Diltiazem	Rifampin
Felodipine,	Ketoconazole	Rifabutin
isradipine	Fluconazole	Phenytoin
Nifedipine	Itraconazole	Corticosteroids
Nisoldipine	Quinidine	Troglitazone
Nitrendipine	Grapefruit juice	St. John's wort
Digoxin, quinidine	Cimetidine	
Verapamil	Indinavir	
Warfarin	Fluoxetine	
Sildenafil	Zileuton, Zafirlukast	
Astemizole	Verapamil	
Terfenadine	Amiodarone	
Pioglitazone		

Cyclosporine

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

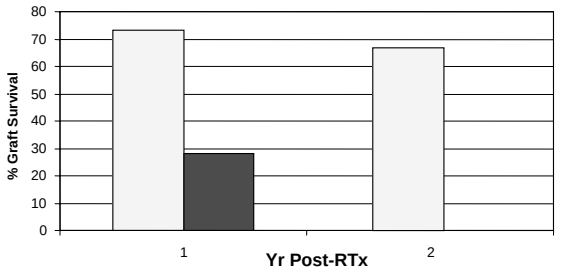
Cyclosporine

- **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

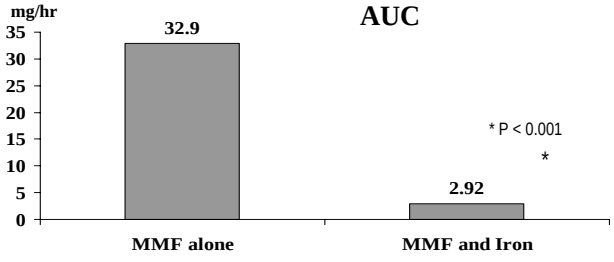
Anticonvulsants and Allograft Survival

n=20 Hx of Seizure and n=92 control



Wassner et. J of Ped 1976;88:134

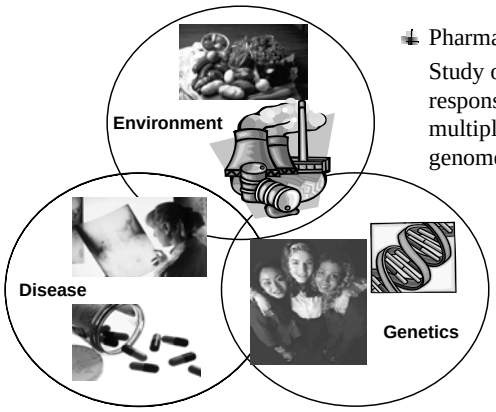
Iron and Mycophenolate



Morii M et al. Clinical Pharmco Ther 2000;68:613

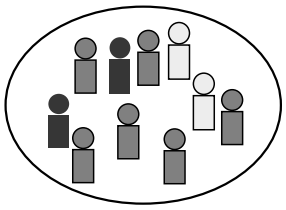
Pharmacogenomics; Going Down the Rabbit Hole

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

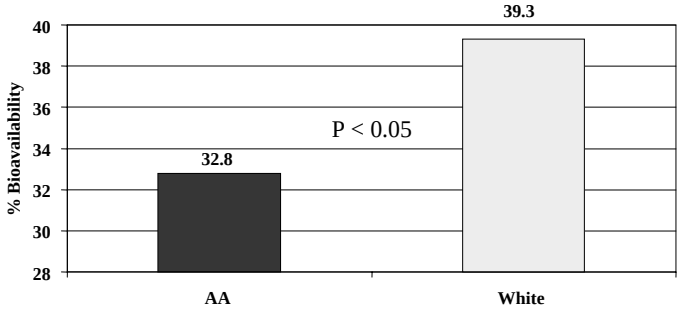


Responders

Non-responders

Toxic responders

African American vs Caucasian Cyclosporine



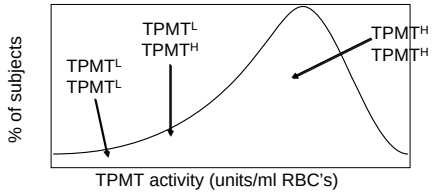
Lee M et al. ***Journal of Clinical Pharmacology, 2001;41:317-323***

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

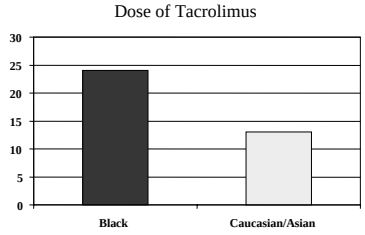
Tacrolimus

- 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**

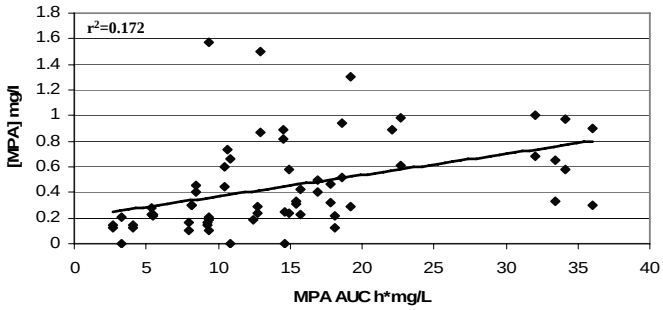


Transplantation. 74(11):1486-1489, December 15, 2002.

Calcineurin Inhibitors: Adverse Effects

	Tacrolimus	CYA
Tremor	54.1%	33.8%
Diabetes	19.9%	4.0%
Hyperlipidemia	7.8%	14.5%
Hirsutism	0.5%	8.7%

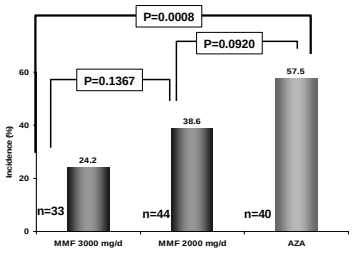
MPA AUC to Trough Correlation



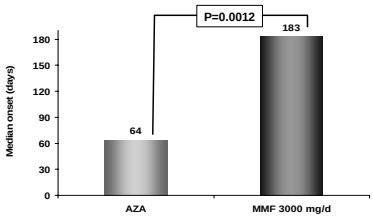
Sievers, et al. Presented at ATC, Seattle, WA 2005

Mourad M, et al. Clin Chem 2001;47:88

Incidence of Acute Rejection Associated With MMF in African American Patients



Biopsy-proven acute rejection and treatment failure

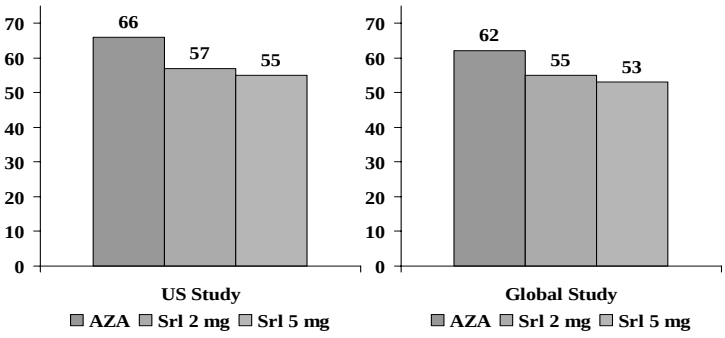


Onset of BPR/TF

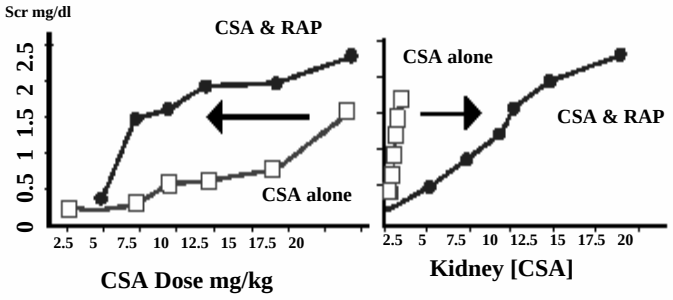
BPR/TF = biopsy-proven rejection/treatment failure.
Patients also received cyclosporine plus corticosteroids plus antithymocyte globulin induction therapy.

Neylan JF et al. *Transplantation*. 1997;64:1277-1282. 40

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

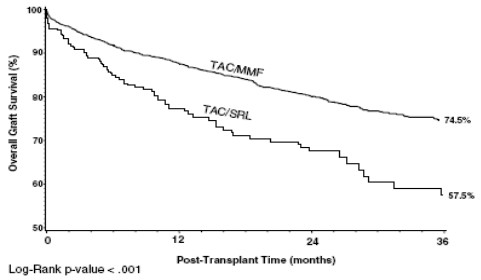


Pharmacodynamic Drug Interactions (CSA and Sirolimus)



Podder et al. J Am Soc Nephrol. 2001 May;12(5):1059-71.

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



* 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

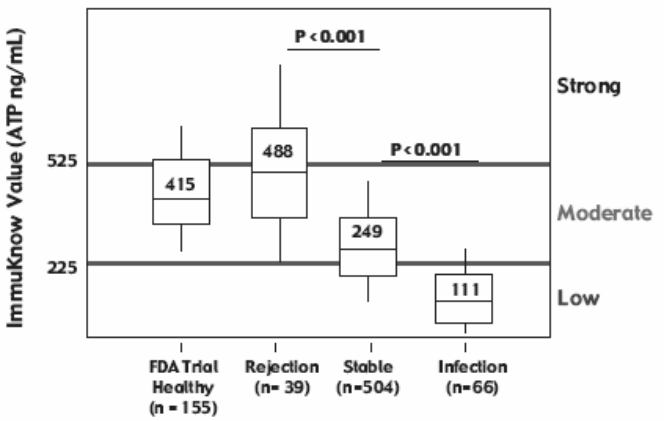
What is a biomarker?

Alternatively:

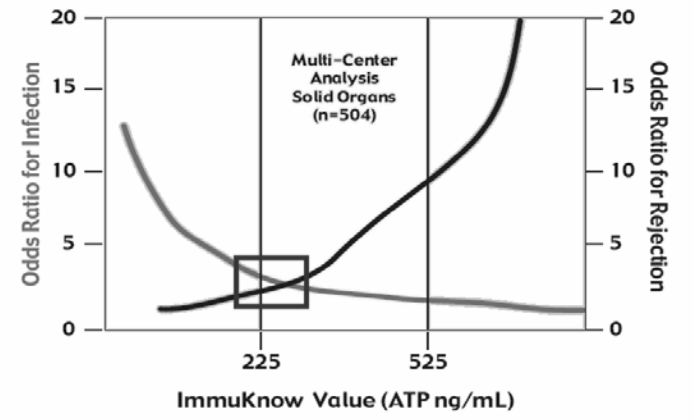
- "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic response(s) to a therapeutic intervention"

-NIH/FDA Biomarkers Definitions Working Group (1999)

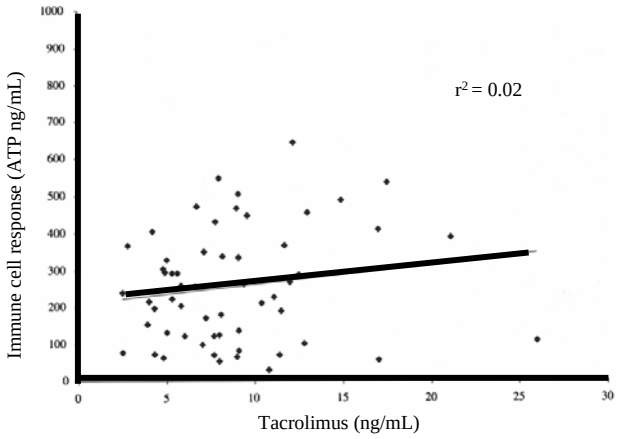
Biomarkers in Transplant Management



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

Federal Register 1997

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 differe 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)

Dose* (day)	500 mg
Amount of active CSA absorbed (30%)	150 mg
Amount of active CSA absorbed (50%)	250 mg
Incremental difference in bioavailiability	±10%
Max. change in mg of cyclosporine	±50 mg/day
Max. mg of cyclosporine absorbed (30%)	±15 mg/day
Max. mg of cyclosporine absorbed (50%)	± 25 mg/day

* CSA dose: 7 mg/kg/day

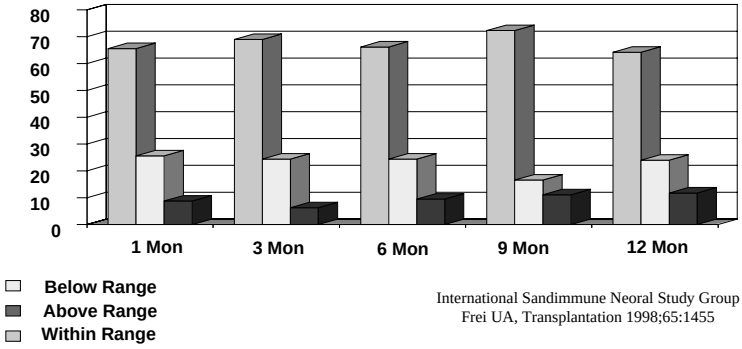
Model for Generic Drugs

Days Post-Transplantation (greater than 6 months)

Dose* (day)	250 mg
Amount of active CSA absorbed (30%)	75 mg
Amount of active CSA absorbed (50%)	125 mg
Incremental difference in bioavailiability	± 10%
Max. change in mg of cyclosporine	±25 mg/day
Max. milligram of CSA absorbed (30%)	±7.5 mg/day
Max. milligram of CSA absorbed (50%)	±12.5 mg/day

* CSA dose: 4 mg/kg/day

Percentage of Patients with Trough Cyclosporine (Neoral) Levels Within, Above or Below the Desired Range



International Sandimmune Neoral Study Group
Frei UA, Transplantation 1998;65:1455

Cost of Immunosuppressive Drugs

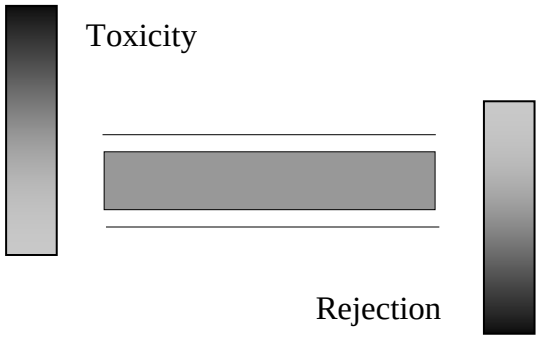
Acquistion Cost	AWP	Non- profit Pharmacy	For-profit Pharmacy	MAC
Neoral 25 mg	1.44	60%	82%	1.41
Sandimmune 25 mg	1.61	58%	81%	1.41
Neoral 100 mg	5.77	65%	82%	5.69
Sandimmune 100 mg	6.40	55%	80%	5.69

AWP: Average Wholesale Price
MAC: Maximum Allowable Cost

Cost of Immunosuppressive Drugs

Acquistion Cost	Non- profit Pharmacy ($)	70 Kg Pt. (daily cost $)	70 Kg Pt. (yearly cost $)	Cost saving ($)
Generic CSA at 75% of AWP	4.32	12.96	4,730	- 613
Generic CSA at 50% of AWP	2.88	8.64	3,157	960
Cost of TDM ($)	70			???

Target Cyclosporine Blood Concentration



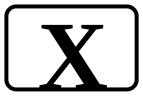
Bioinequivalence and Drug Toxicity

Drug	Clinical Outcomes	Ref.
Digoxin	Intoxication	*Clin Pharmaco Ther 1977;21:643*
Phenytoin	Intoxication	*BMJ 1971;2:271*
Amitriptyline	Lack of effect	*Am J Psych 1979;136:4 A*
Carbamazepine	Lack of effect	*Lancet 1987;1:1432*
Cyclosporine	Rejection	*?????*

Drug Safety 1994;11:1

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 is right.

Martin Luther King, Jr., 1968

Growing old is mandatory, growing wise is optional