Drug Interactions in Stem Cell Transplantation

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Learning Objectives
- Explain the common metabolic pathways in the liver
- Identify approaches to overcome drug interactions seen in HSCT
  - Identify those drug interactions of importance
  - Understand how to preemptively prevent drug interactions from occurring

When is a drug interaction in HCT recipients important?
- Drug interaction leads to an undesired outcome, whether it be ↓ efficacy or ↑ toxicity
- Type of interactions
  - Pharmaceutical
  - Pharmacokinetic
  - Pharmacodynamic

The challenges unique to HCT patients are …..
- The concentration-effect (i.e., pharmacodynamic) relationships are rarely defined
- Degree of an interaction (and thus its significance) rarely described
  - Cytokines influence regulation
  - Interpatient variability in the interaction
- When an adverse drug interaction occurs, we often lack the pharmacokinetic data to explain it

Quick review of pharmacokinetic-based drug interaction basics
- Drug metabolizing enzymes
- Drug Transporters
Relationship between Pharmacokinetics and Pharmacodynamics

Dose

Absorption
Distribution
Metabolism
Excretion

Total serum concentration
Unbound serum concentration
Protein Bound Concentration

Receptor Site
Pharmacologic Response
Therapeutic Outcome

Rational Use of Drugs in Patients

What the body does to the drug – pharmacokinetics

What the drug does to the body – pharmacodynamics
Safety and efficacy

Pharmacology is Multifactorial

Can affect both the pharmacokinetics and pharmacodynamics
Factors include...
- Age
- Sex
- Ethnicity
- Weight
- Condition being treated
- Pharmacogenetics
- Idiosyncrasy
- Drug interaction

Pharmacokinetic Parameters

Absorption
- The rate at which a drug leaves the site of administration and the extent to which it occurs.

Distribution
- Process of reversible transfer of a drug to and from the site of measurement.
- Modifying factors:
  - blood flow
  - plasma protein binding
  - diffusion
  - solubility

Volume of Distribution

A measure of the apparent space in the body available to contain the drug.
Relates the amount of drug in the body to the concentration of drug in the blood.

\[ Vd = \frac{\text{Amt of drug in body}}{\text{Conc. of drug in blood}} = \frac{\text{Dose}}{\text{Concentration}} \]

Elimination Processes

Metabolism
- Predominately liver
- Other sites: kidney, lung, GI, plasma

Excretion
- Kidneys and GI
- Other sites: milk, sweat, saliva, tears
Biotransformation (Metabolism)

- **Theory:**
  - Drug inactivation
  - Increased elimination from the body

- **However:**
  - Metabolites may have biological activity; similar or different than parent
  - May contribute to toxic and/or beneficial effects

Phase I metabolism:

- Oxidation, reduction, hydrolysis
- Cytochrome P450 family of enzymes
  - 7 primary enzymes responsible for majority of drug metabolism:
  - Can predict drug interactions based on knowledge of metabolites
    - CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4

The Cytochrome P450 (CYP) Enzyme System

- **Phase I enzymes**
  - Liver
    - Several different isozymes located in endoplasmic reticulum
    - e.g., CYP1A2, CYP2A6, CYP2B6, CYP2C, CYP3A
  - Extrahepatic: intestine (CYP3A4/5), kidney (CYP3A5), brain (CYP2B6), lungs, breast
  - Large source of drug interactions
  - Differences in enzyme regulation between animals – humans
  - Variety of in-vitro methods
    - Inhibition: cDNA expressed or human microsomes
    - Induction: human hepatocytes or some constructed cell lines
  - In-vivo methods
    - Healthy volunteer studies with ‘cocktails’ largely used but effects of cytokines (e.g., IL6) upon PXR function which contributes to regulation of CYP3A/CYP2B6/pgp induction

Examples of important CYP in HCT

<table>
<thead>
<tr>
<th>Drug</th>
<th>Substrate for Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide (CY)</td>
<td>Activation to 4hydroxyCY (HCY)</td>
</tr>
<tr>
<td>2C9, 2C19</td>
<td></td>
</tr>
<tr>
<td>2B6, 3A4/5</td>
<td></td>
</tr>
<tr>
<td>3A4/5</td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>Detoxification to dechloroCY</td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3A4/5</td>
<td>Elimination</td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
</tr>
<tr>
<td>3A4/5</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
</tr>
<tr>
<td>3A4/5</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
</tr>
<tr>
<td>3A4/5</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
</tr>
<tr>
<td>3A4/5</td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td></td>
</tr>
<tr>
<td>3A4/5</td>
<td></td>
</tr>
</tbody>
</table>

*Models. I: in vitro; HV: PK study in healthy volunteers; C: PK study in cancer patients

Effect upon CYP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Model</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CY</td>
<td>↓ CYP3A4, CYP2B6 I</td>
<td>Lindley Drug Metab Disp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ CYP3A4 I</td>
<td>Moore Clin Pharmacol Ther</td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>↓ CYP2C9, CYP2D6 I</td>
<td>Package insert</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CYP3A4/5 I, HV</td>
<td>O'Brien Br J Cancer 2003</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>↑ CYP3A4/5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEX</td>
<td>↑ CYP3A4/5 I, HV</td>
<td>McCune Clin Pharm Ther</td>
<td></td>
</tr>
</tbody>
</table>

Phase II Metabolism

- Term coined to represent metabolism occurring after oxidation, reduction or hydrolysis associated with bioactivation
- Many drugs don’t require Phase I metabolism
- Functional group created conjugated to less toxic or inactive compound
Phase II: Conjugation reactions

- Acetylation (Procainamide, sulfonamides)
- Glutathione S-transferase
  - Mediate conjugation of electrophilic compounds to glutathione
  - Important detoxifying pathway for alkylating agents
- Glucuronidation
  - Most common conjugation reaction for drugs
  - UGT (UDP-glucuronosyl transferase)
  - Conjugation of endogenous substances, bilirubin, mycophenolic acid, morphine
- Sulfation

ATP-binding cassette (ABC) superfamily

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCB1 (MDR1)*</td>
<td>calcineurin inhibitors, sirolimus</td>
</tr>
<tr>
<td>ABCC1 (MRP1)</td>
<td>etoposide, glutathione conjugates of corticosteroids</td>
</tr>
<tr>
<td>ABCC2 (MRP2)</td>
<td>CPM (CY metabolite), Mycophenolic acid</td>
</tr>
<tr>
<td>ABC C3, C4, C5</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>ABCG2 (BCRP)</td>
<td></td>
</tr>
</tbody>
</table>

*codes for p-glycoprotein (pgp)

Additional Transporters

- Organic anion transporting polypeptide (OATP)
  - Methotrexate, opioids, corticosteroid metabolites
- Organic anion transporters (OAT)
  - Beta-lactams, metabolites of corticosteroids, NSAIDs
- Equilibrative nucleoside transporter 1 (ENT)
  - Fludarabine
- Concentrative pyrimidine-preferring nucleoside transporter 1 (CNT)

Excretion

- Drugs are eliminated from the body unchanged or as metabolites
- Polar > > > > > Lipid soluble drugs
- Involves
  - Glomerular filtration
  - Active tubular transport
  - Passive tubular absorption

Clearance

- A measure of the body’s ability to eliminate drugs.
- May be regarded as the volume from which all the drug would appear to be removed per unit time.
- Clearance is the PK parameter most useful for evaluation of an elimination mechanism.
- Described in terms of eliminating organ
  - Hepatic clearance
  - Renal clearance
  - Pulmonary clearance

Elimination Half-Life

- The time is take for the amount of drug in the body to be reduced by 50%.
- \[ T_{1/2} = \frac{0.693 \cdot V_d}{Cl} \]
  - where \( V_d \) = volume of distribution
  - \( Cl \) = total body clearance
Elimination Half-life
Example: Plasma Concentrations Drug with $T_{1/2} = 12$ hrs

<table>
<thead>
<tr>
<th>Dose</th>
<th>100 mg</th>
<th>200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_0$</td>
<td>20 µg/ml</td>
<td>40 µg/ml</td>
</tr>
<tr>
<td>$C_{12hr}$</td>
<td>10 µg/ml</td>
<td>20 µg/ml</td>
</tr>
<tr>
<td>$C_{24hr}$</td>
<td>5 µg/ml</td>
<td>10 µg/ml</td>
</tr>
<tr>
<td>$C_{36hr}$</td>
<td>2.5 µg/ml</td>
<td>5 µg/ml</td>
</tr>
<tr>
<td>$C_{48hr}$</td>
<td>1.2 µg/ml</td>
<td>2.5 µg/ml</td>
</tr>
<tr>
<td>$C_{60hr}$</td>
<td>&lt; 1 µg/ml</td>
<td>1.2 µg/ml</td>
</tr>
<tr>
<td>$C_{72hr}$</td>
<td>&lt; 1 µg/ml</td>
<td>&lt; 1 µg/ml</td>
</tr>
</tbody>
</table>

Steady State

- $C_{ss}$ = the concentration at which the rate of drug input is equal to the rate of drug elimination
- Can be defined as area under the curve/dosing interval (busulfan)
- Takes approximately 5 $T_{1/2}$ to reach steady state
- Take approximately 5 $T_{1/2}$ to completely eliminate a drug after discontinuation
- $C_{ss}$ is dependent on dosage and clearance

Learning Objectives

- Explain the common metabolic pathways in the liver
- Identify approaches to overcome drug interactions seen in HSCT
  - Identify those drug interactions of importance
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GVHD Medications

- Cyclosporine, Tacrolimus, Mycophenolate mofetil, Methotrexate, Sirolimus, Prednisone

Less commonly used GVHD medications

- Immunomodulating modalities: mTOR-inhibitors, thalidomide, hydroxychloroquine, vitamin A analogs, clofazimine, rituximab, alemtuzumab, etanercept
- Cytostatic agents: mycophenolate mofetil, methotrexate, cyclophosphamide, pentostatin

The interactions discussed

- Pharmacokinetic interactions relevant to GVHD prophylaxis and treatment
  - Will discuss herbal preparations, but recall they are unique because of potential pill to pill variability in content, for fungal contamination, immunologic properties.....
  - Omitting others not because they are less important but they may be
    - more easily identified (e.g., the opioids because of close concentration - effect relationship)
    - more broad therapeutic index of the medication (e.g., most antibiotics)
Effect of food/herbs

<table>
<thead>
<tr>
<th>AED</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grapefruit juice</td>
<td>↓ intestinal CYP3A, ↔ pgp</td>
</tr>
<tr>
<td>Phytoestrogens/flavonoids</td>
<td>competitively ↓ABCG21</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>↑ CYP3A4, pgp</td>
</tr>
<tr>
<td>Garlic</td>
<td>↑ CYP3A4</td>
</tr>
</tbody>
</table>

Calcineurin Inhibitors

- Pharmacodynamic relationships
  - ↓CyA/TAC ↓risk of aGVHD
  - ↑CyA/TAC ↑nephrotoxicity
    - occurs even with targeting trough CyA or TAC trough concentrations

- Substrates for CYP3A4/CYP3A5 and p-glycoprotein

Calcineurin Inhibitors

- Personalized through trough concentrations of cyclosporine or tacrolimus, but considerable interpatient variability in efficacy and toxicity remain
  - Cyclosporine concentrations poorly correlate with calcineurin activity in HCT and kidney transplant recipients
  - Calcineurin activity higher in kidney transplant patients receiving tacrolimus vs. cyclosporine
  - Calcineurin activity
    - Methods available for over 15 years, with some recent methodologic advances
    - But, calcineurin activity, assessed using the newer methods, have yet to be associated with clinical outcomes in solid organ transplant recipients
    - Within HCT recipients, two studies have conflicting findings regarding the association between CYP content and acute GVHD

Pharmacogenomics of renal dysfunction in HCT patients receiving calcineurin inhibitors

- Various pharmacogenomic associations found in solid organ transplant patients
- ABCB1 and CYP3A5 responsible for the renal disposition of calcineurin inhibitors
- Investigated pharmacogenomic associations in the multidrug resistance (ABCB1) and cytochrome P450 3A5 (CYP3A5) genes and acute kidney injury (AKI) and chronic kidney disease (CKD) in 121 CY/TBI conditioned patients
- No pharmacogenomic associations found
- Patients genotyped for CYP3A5*1>*3 and ABCB1 single nucleotide polymorphisms (SNPs, 1199G>A, 1236C>T, 2677G>T/A and 3435C>T).
- AKI occurred in 48 of 121 patients (39.7%) and CKD in 16 of 66 patients (24.2%)
- Haplotype estimation and univariate association analyses performed because of strong ABCB1 linkage disequilibrium

Variability in CYP3A content


P-glycoprotein

- ATP-dependent drug transporter (ABCB1)
- Transports a large number of structurally diverse agents primarily cationic or neutral hydrophobic drugs
- Limits oral drug bioavailability
- Transports drugs out of renal tubular epithelial cells and mesangial cells on the glomerulus

**P-glycoprotein**

- **P-gp mRNA High**
  - Kidney, Adrenal
- **P-gp mRNA Intermediate**
  - Liver, Lung
  - Jejunum, Colon, Rectum
  - Lymphoid bone marrow & T-cells
- **P-gp mRNA Low**
  - Brain, Spleen
  - Prostate, Ovary
  - Muscle, Skin
  - Stomach, Esophagus


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**Medication that increase CyA or TAC plasma concentrations**

<table>
<thead>
<tr>
<th>Agent</th>
<th>CYP3A Effect</th>
<th>pgp Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Clarithromycin, Erythromycin</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Diltiazem, Nicardipine, Verapamil</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Fluconazole, Itraconazole, Ketoconazole, Voriconazole</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Grapefruit Juice</td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Theophylline</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Imatinib</td>
<td>↓</td>
<td>?</td>
</tr>
</tbody>
</table>

**Management:** Monitor concentrations, ↓ dose of CNI PRN


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**Medication that decrease CyA or TAC plasma concentrations**

<table>
<thead>
<tr>
<th>Agent</th>
<th>CYP3A Effect</th>
<th>P-gp Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Rifampin</td>
<td>↑</td>
<td>↑↓</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>CV/cytarabine</td>
<td>↑ (?)</td>
<td>?</td>
</tr>
</tbody>
</table>

**Management:** Monitor concentrations, ↑ dose of CNI PRN


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**Interactions**

- **Drug-drug interactions**
  - Cyclophosphamide
    - Activated by cytochrome P450, thus inhibitors would decrease HCY. Itraconazole ↑ exposure to metabolites associated with hepatotoxicity
  - Cyclosporine increases mycophenolic acid clearance

- **Drug-food Interactions:**
  - Grapefruit juice inhibits CYP3A4 and thus ↑ sirolimus absorption
  - Not always predictable. Expect grapefruit juice to ↑ absorption of etoposide, a CYP3A4/pglycoprotein substrate, but it actually decreased the absorption in cancer patients.


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**Methotrexate**

- **Pharmacodynamics**
- **Interactions**
  - Avoid salicylates, NSAIDs and probenecid
  - ↑ nephrotoxicity, bone marrow suppression, mucositis
  - TMP/SMX, penicillins

Reference: McDonnell (Hansten & Horn; Dorr)

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**Mycophenolate Mofetil (MMF)**

- **Pharmacodynamic relationships**
  - being identified in HCT patients
- **Cholestyramine**
  - ↓ MPA AUC 40% (10-61%)
  - Avoid this combination
- **Norfloxacin/metronidazole**
  - ↓ enterohepatic recirculation ↓ MPA AUC by 30%

Reference: McDonnell (Hansten & Horn; Dorr)
Pharmacodynamics After MMF Administration to HCT Patients

- Evaluated in heterogeneous populations, differing by recipient age, conditioning regimen, graft sources
- Acute GVHD associated with low total MPA trough concentrations or low free MPA AUC (but not trough) ¹
- Graft rejection associated with low total MPA trough concentrations or total MPA Css (but not trough) ²
- Low T cell chimerism associated with low total MPA Css ³


MPA Pharmacodynamics in Nonmyeloablative, Unrelated Donor HCT

- 85 patients, hematologic malignancies, FLU/TBI, HLA-matched unrelated-donor, cyclosporine/MMF post-grafting
- 16 patients with a total MPA Css <3 µg/mL had low (<30%) donor T-cell chimerism (P = .03)
- Only modifiable risk factor for donor chimerism
- 6 patients with MPA Css <2.5 µg/mL had graft rejection
- Elevated unbound Css was associated with CMV reactivation (20 vs 31 ng/mL, P = .03)
- No significant associations with acute GVHD or relapse


Mycophenolate Mofetil Drug Interactions

- Antacids (Magnesium and Aluminum Hydroxides)¹
  - ↓ MPA Cmax by 33% & ↓ 24 hour AUC 17%
- Ferrous Sulfate
  - ↓ MPA AUC 90% in one cross-over study, but another study in renal transplant patients suggests no interaction ²
- Calcium Polycarbophil (e.g. Fibercon)
  - ↓ MPA AUC 25-50%
- No effect on TMP/SMX, acyclovir, ganciclovir, oral contraceptives ³


Mycophenolate Mofetil Drug Interactions

- CyA
  - ↓ AUC of MPA and ↑ AUC of MPA glucuronide
  - Disrupts enterohepatic recirculation by affecting transport
- TAC
  - May inhibit UGT
  - Management: If switch from CyA to TAC, ↓ MMF dose

Sirolimus

- Substrate for CYP3A4/5 & p-glycoprotein
  - Similar drug interactions as tacrolimus and cyclosporine
- Effect of other immunosuppressants upon sirolimus dose-normalized Ctrough
  - not affected by methylprednisolone pulses (500-3000 mg)
  - higher in patients on cyclosporine vs. tacrolimus

Sirolimus-Neoral

Sirolimus

- Substrate for CYP3A4/5 & p-glycoprotein
- Factors important in drug interactions similar to those important for tacrolimus and cyclosporine
- Dose-normalized Ctrough higher in patients on cyclosporine vs. tacrolimus

Corticosteroids

- In general, steroid metabolism involves sequential hydroxylation followed by conjugation to water-soluble metabolites
- Urinary elimination of the 6β-hydroxy metabolites makes up 8-10% of the dose for prednisone
- 6β-hydroxylation occurs via CYP3A4 and CYP3A5 but is a relatively minor pathway
- P-glycoprotein appears to be involved in the transport of some steroids (cortisol, dexamethasone, methylprednisolone)

Corticosteroid Drug Interactions

- Increase Levels
  - Ketoconazole
  - Oral Contraceptives
- Decrease Levels
  - Phenytoin
  - Phenobarbital
  - Carbamazepine
  - Rifampin

Effects of dexamethasone upon CYP3A/pgp

Haploidentical Donors

- Virtually all have one haplotype-mismatched donor
  - Can select from best of any relatives based on age, infectious disease status, and natural killer (NK) reactivity
  - Immediate access to donor-derived cellular therapies
- In 1980s, mortality risk was too high
- Recent interest due to improved patient selection (by disease and genetics), supportive care, and GVHD prophylaxis
Umbilical Cord Blood

- Use in adults limited by small cell dose, resulting in delayed engraftment
- Double cord blood leads to rapid neutrophil recovery with one single cord ultimately "winning"
- Have increased incidence of acute GVHD, long-term thrombocytopenia in subset of patients
- Many unanswered questions about HLA matching, RIC, minimum cell dose, immune reconstitution, ex vivo expansion


Cyclophosphamide

- Urine
- DichloroethylCY + CAA
- CYP3A
- CEPM
- ALDH1A1
- IminoCY
- HCY
- AldoCY
- 4-gluthionylCY
- Phosphoramide
- Mustard
- Acrolein


CY Pharmacodynamics Differ With Conditioning Regimens

- With TBU/CY, there were no statistically significant associations between the AUC of CY or its metabolites and liver toxicity, non-relapse mortality, relapse, or survival (all P > .15)
- Oral busulfan doses targeted to Css 800-900 ng/mL
- Personalization of CY doses based on its pharmacokinetics in TBu/CY unlikely to be beneficial
- CY, like busulfan, pharmacodynamics differ between conditioning regimens
- Lower toxicity by using bu/fludarabine regimen?


Reported interactions with CY

- CY autoinduces clearance
- Significance unknown
- Thiopeta ↓ CYP2B6
- CY half-life1: ↑ by eltopurinol, ↓ by barbiturates, corticosteroids
- ↓ alkylation activity: barbiturates, AED1
- Ondansetron: ↓ CY AUC in CPB regimen2
- Aprepitant: moderate CYP3A4 inhibitor, mild CYP2C9 and CYP2C19 inhibitor...no effects on CY to HCY formation
- In-vitro: DEX, phenobarb, rifampin ↑ HCY formation


CY-itraconazole interaction

- Itraconazole (200 mg IV QD, or oral solution 2.5 mg/kg TID)
- fluconazole (400 mg IV/PO QD)
- Patients who received itraconazole developed higher serum bilirubin and creatinine values in the first 20 days after SCT
- highest values in patients who received itraconazole concurrent with CY


CY Pharmacokinetics Depend on Conditioning Regimen

- TBu/CY N=75
- CY/TBI N=147

Conclusions

- Drug interactions are frequent in HCT patients
- Changes in CYP cause many pharmacokinetic drug interactions, but other types of interactions are also relevant
- Within GVHD prophylaxis, the routine use of monitoring for calcineurin inhibitors can guide management.
- Further pharmacodynamic data needed to know impact of interactions with mycophenolate mofetil, corticosteroids and sirolimus